1.8 DRUG INTERACTIONS

Drug interactions occur on simultaneous use of two or more drugs. When two drugs are administered in close sequence to each other, they may interact either to ***enhance*** or ***diminish*** the intended effect of one or both drugs, or they may produce an unintended and potentially harmful reaction. Unfortunately drug interactions may be recognized only when severe toxicity occurs, *e.g.*, a hypertensive crisis may occur when a monoamine oxidase inhibitor (MAOI) like *tranylcypromine*, and an indirectly acting sympathomimetic drug like *methamphetamine* are used together; severe haemorrhage may occur if *warfarin* and *salicylates* are combined.

Definitions

The term ***drug interaction*** is defined as an alteration in the *duration* or *magnitude* (or both) of the pharmacological effect of one drug produced by another drug. When more than one drug is administered simultaneously the combined effect may be *antagonistic* or *synergistic*. In ***antagonism*** the effect of one drug is reduced or abolished by the other, whereas, in synergism the effects may be ***additive*** or ***supra-additive*** (potentiation). Apart from these phenomena numerous drug interactions are harmful and severe toxic reactions may occur. The incidence of such reactions has increased mainly due to three factors (*i*) ***drug explosion;*** (*ii*) ***availability of potent drugs;*** and (*iii*) ***irrational polypharmacy,*** *i.e.*, indiscriminate prescribing of combined preparations by the clinician (iatrogenic or doctor-induced diseases).

The term ***polypharmacy*** covers the practice of multiple drug therapy in the management of disease. Judicious use of drug combinations (*rational polypharmacy*) can be of considerable benefit to the patient for the following reasons :

1. To produce a *synergistic* effect which is not obtained by one drug alone, *e.g.*, *hydrochlorothiazide* plus *hydralazine* plus *propranolol* in severe hypertension; combination of *isoniazid*, *rifampicin* and *ethambutol* in tuberculosis.
2. To *minimize side effects of drugs*, *e.g.*, potassium supplementation or *potassium sparing diuretics* in patients on potent diuretic and digitalis therapy; addition of a diuretic to overcome salt and water retention caused by methyldopa.
3. Several *diseases may coexist*, specially in the elderly, and each requires treatment, *e.g.*, association of *hypertension*, *coronary artery disease*, *diabetes mellitus* and *arthritis*. Therapy has to be judiciously chalked out to minimize untoward effects. The benefit-to-risk ratio is of critical importance in such cases.

It must be stressed that multiple drug therapy can be very useful, but the risks involved in the treatment increase. Greater the number of drugs used together, greater the risk of serious adverse reactions.

Factors Predisposing to Drug Interactions

Many adverse drug interactions can be avoided if the following predisposing factors are kept in mind:

1. *Insufficient knowledge.* Effective and safe combination drug therapy requires adequate understanding of the pharmacokinetics and pharmacodynamics of the drug. This only can enable the prescriber to select the proper drug combination.
2. *Dietary factors.* Constituents of an individual's diet can interact with certain drugs, *e.g.*, MAOIs interact with tyramine-containing food stuffs inducing a hypertensive crisis; green leafy vegetables decrease the anticoagulant response of coumarin anticoagulants as they contain vitamin K. Some drug-food interactions are summarized in **Table 1.8-1.**

Table 1.8-1. *Some important drug-food interactions*

Drug	*Food Item*	*Effect*
Anticoagultants	Food rich in vitamin K (*e.g.*, egg yolk, citrus fruits, green leafy vegetables)	Decreased anticoagultant response due to enhaced hepatic synthesis of clotting factors.
Antihypertensives, diuretics	Licorice (glycyrrhizic acid)	Causes hypokalaemia, sodium retension, elevated blood pressure
Digoxin	Milk products	Slowed gastric absorption and decreased therapeutic effect
Erythromycin	Acidic fruit juices	Decompose the drug and reduce effect
Griseofulvin	High fat content	Increased absorption rate
MAOIs (pargyline, phenelzine)	Food rich in tyramine (*e.g.*, cheese, red wine, chicken liver)	Hypertensive crisis
Paracetamol	Carbohydrates	Slow drug absorption and therapeutic effect
Quinidine	Basic foods (*e.g.*, milk, nuts, most vegetables)	Decreased renal clearance due to increased urine alkalinity, toxic reaction may occur
Tetracycline	Milk products containing Ca^{++}	Decreased gastrointestinal absorption and drug inactivation

3. *Physiology of the individual.* Factors such as age, sex,

Table 1.8-2. *Some over-the-counter (OTC) medicaments that can interact with prescription drugs*

OTC medicaments	*Major interactants*
Analgesics	
Paracetamol	Increased hepatotoxicity of other drugs that also damage the liver
Salicylates (aspirin)	Increased bleeding with anticoagulants and other platelet inhibitors; increased GI ulceration with other gastric irritants (corticosteroids, anti-inflammatory agents); potentiation of oral antidiabetics, barbiturates, phenytoin, and sulphonamides by displacing them from protein binding; decreased effectiveness of vitamin C by increasing its excretion
Antacids	Impaired absorption of many drugs
Anticholinergics (atropine, scopolamine)	Increased side effects (dry mouth, blurred vision, constipation) of other drugs having anticholinergic activity (antihistamines, tricyclic antideprebsants, carbamazepine, disopyramide)
Antidiarrhoeals	Decreased absorption of many drugs by slowing GI motility
Antihistamines	Increased sedative effect of CNS depressants; increased anticholinergic effect of other anticholinergics
Bronchodilators (adrenaline, ephedrine)	Increased hypertensive effect of pressor agents; decreased effect of oral antidiabetics; increased toxicity of digitalis
Decongestants (Phenylephrine, pseudoephedrine)	Decreased effectiveness of antihypertensives; increased danger of hypertension with MAOIs, other vaspressors and CNS stimultants like amphetamine
Expectorants (guaifensin)	Increased risk of haemorrhage with heparin
Vitamin B_6 (Pyridoxine)	Decreased effectiveness of levodopa
Vitamin B Complex	Increased risk of bleeding by increasing prothrombin time
Vitamin C	Decreased excretion of weak acids (barbiturates, salicylates, sulphonamides); increased excretion of weak bases (amphetamine, atropine, quinidine).

weight and genetic abnormalities influnece the occurance of drug interactions. These factors have been discussed in **Chapter 1.4 and 1.7.**

4. *Presence of disease states.* Pathologic conditions like liver disease, kidney damage, or altered enzyme systems may affect the handling of drugs by the body. This can lead to adverse drug reactions. **(Chap. 1.7).**
5. *Patient behaviour.* The common practice of consulting more than one physician at a time can increase the risk of drug interactions, if each prescriber is not fully aware of the drugs being taken by the patient. *Self-medication* is also responsible for a number of drug interactions, and can be avoided by proper counselling. Similarly, the large number of over-the-counter (OTC) preparations can interact with prescription drugs. **Table 1.8-2** lists some OTCs which can interact with prescribed drugs. In addition, certain factors like poor *compliance* (failure to take the medication as directed); *smoking* (increases metabolism of many drugs); *excessive alcohol consumption* (altered drug metabolism and potentiation of the action of CNS depressants); and use of *dependence producing drugs* are examples of human behaviour which may lead to drug interactions.
6. *Enviromental factors.* Small amounts of insecticides, fungicides, or industrial wastes can markedly alter the effect of certain drugs, *e.g.*, chlorinated insecticides stimultate drug metabolism by liver enzymes; some pesticides are cholinesterase inhibitors and serious toxicity (respiratory distress, skeletal muscle weakness, convulsions) can occur in cases of poisoning by another cholinergic drug.
7. *Dosage form factors.* Incompatibilty of different dosage forms may result in drug interactions at either a *physical* or a *chemical* level. Generally, the main factor in this regard is of *bioavailability, i.e.*, what fraction of the dose is available through absorption at the site of action. Of particular concern in this regard are the many "long-acting" or "sustained-release" dosage forms currently available. Many of these products are tablets or capsules that dissolve slowly over many hours, providing a sustained release of medication for a certain period of time, and fairly stable plasma levels are maintained. This steady-state plasma concentration can be upset by the presence of another drug which increases gastrointestinal motility and peristalsis. As a result the sustained-release dosage form traverses the intestine too quickly to provide for a prolonged drug effect.

Some over 1600 potential drug interactions have been described in man. Many of them are of great clinical significance. It is impossible to remember them, but ready information is available in pocket books, manuals on drug interactions, drug interaction discs, slide rules or from hospital drug information centres. However, it is helpful to be aware of the various sites at which drug interactions can occur, and the broad mechanisms involved. Harmful interactions can occur between *drug–drug; drug–patient–drug;* and *drug–foodstuffs.*

Classification and Mechanisms of Drug Interactions

Drug interactions may occur ***outside the body*** (*in vitro*) or ***inside the body*** (*in vivo*). Any classification of drug interactions would be an over-simplifcation, but the following outline will serve as an aid in categorizing them according to the mechanism involved:

I. *Outside the body (in vitro)*
   1. Physical
   2. Chemical

II. *Inside the body (in vivo)*
   1. Pharmacokinetic interactions
   2. Pharmacodynamic interactions

Table 1.8-3. *Drug interactions which result in altered absorption from the gastrointestinal tract*

	Interacting drugs	*Result of interaction*
1.	Antacids with anticoagultants like dicoumarol and warfarin	Antacids interfere with the absorption resulting in the antagonism of anticoagulant action
2.	Antacids with certain anti-infective agents like sulphonamides, nalidixic acid and nitrofurantion	Antacids interfere with absorption of these weakly acid agents resulting in a reduction of their activity
3.	Antacids (and milk) with tetracycline	Calcium, magnesium and aluminium ions tend to bind tetracyclines in poorly absorbable complexes
4.	Mineral oils and fat soluble vitamins (A, D, E, K)	Mineral oil reduces the absorption of fat-soluble vitamins
5.	Cholestyramine with vitamins A, D and K; also anticoagulants; possibly other weakly acid drugs like chlorothiazide and phenylbutazone	Cholestyramine (anion exchange resin) has a strong affinity for acidic substances. Binding of these drugs results in their faecal excretion and poor systemic absorption

Outside the Body

These interactions may occur during formulation and mixing of drugs, and the term ***incompatibility*** is often used to designate these *in vitro* interactions. They may either be *physical* or *chemical* in nature.

1. ***Physical interactions.*** This term applies when the physical state of either drug is altered when the chemicals are mixed *e.g., amphotericin* precipitates if mixed with normal saline instead of 5 per cent dextrose; the anticoagulant effect of *heparin*, a negatively charged acid is antagonized by protamine, a positively charged base.
2. ***Chemical interactions.*** This term applies when the components of a drug mixture interact to form chemically altered products, *e.g.*, drugs mentioned below are chemically incompatible in solution; methicillin and kanamycin; aminophylline and chlorpromazine; dopamine and sodium bicarbonate; furosemide and ascorbic acid. In most cases chemical incompatibilities are manifested by precipitation or colour change. Occasionally *in vitro* interactions can occur without any observable change.

General guidelines to avoid such interactions occuring *in vitro*: (*i*) Do not add drugs to blood or amino acid solutions; (*ii*) In the absence of special knowledge, a drug should only be added to simple solutions (normal saline, dextrose, dextro-saline). It should be remembered that these solutions have very little buffering capacity; (*iii*) Interactions may occur without any visible changes in the solution; (*iv*) Drugs should be mixed with the infusion fluid immediately before use; (*v*) Single drug additions to simple solutions are likely to be safe, while two or more drugs are likely to interact; and (*vi*) Drug firm package inserts should be consulted, as they contain useful information on likely drug interactions.

Inside the Body

Most of the drug interactions occurring inside the body can be categorized as either *pharmacokinetic* or *pharmacodynamic* interactions.

Pharmacokinetic Interactions

In this category the change in response to the first drug is the result of an alteration in the concentration of the drug at the receptor site, and is produced by differences in drug *absorption, distribution, metabolism* and *excretion*.

Interactions During Gastrointestinal Absorption

Many factors influence drug absorption from the digestive tract, which include *dissolution rate* of the ingested drug, *gastric emptying time, gut motility* and *blood flow*. Drugs are absorbed mainly in their non-ionized form from the gut. Many drugs are weak acids or weak bases, and the proportion of ionized to non-ionized drug is dependent on the pKa value of the drug and surrounding pH **(Chap.1.5).**

Gastric emptying time and gut motility are important factors which determine the rate and extent of absorption of drugs. Decreased gut motility by anticholinergic agents like *atropine* increases the total absorption of drugs which are otherwise slowly and incompletely absorbed. The *purgatives* decrease drug absorption by speeding the passage of material through the intestine.

Antacids that contain calcium, magnesium or aluminium (polyvalent cations), interfere with the absorption of ***tetracycline*** which forms a chelate with these metals. ***Cholestyramine*** which is used to treat certain types of hyperlipidaemias adsorbs drugs like ***warfarin*** and ***thyroxine*** thereby interfering with their absorpiton. Some important interactions are summarized in **Table 1.8-3.**

Interactions During Distribution
Plasma Protein Binding

When certain drugs are absorbed into the blood stream, most of their molecules attach themselves to plasma proteins. The portion of the drug which is being transported in the *bound* form is pharmacologically inactive, and only the *free* molecules that diffuse into the tissue exert their effect. The presence of a second drug with a *higher affinity* for protein, competes with the first drug for protein binding sites, and displaces the first drug, producing serious toxicity, *e.g.*, ***warfarin*** is 98 per cent protein bound, and only 2 per cent is free in the plasma which is the active fraction. If another drug like ***phenytoin*** is given, competition for the binding sites occurs and warfarin is displaced. If the binding of warfarin is reduced to 96 percent, it would lead to doubling (2% unbound to 4% unbound) of the free concentration of the drug leading to toxicity. **Tolbutamide** can be displaced by **dicoumarol** resulting in servere hypoglycaemia. Certain drugs which have a higher binding affinity to plasma proteins displace agents with lower binding affinites **(Table 1.8-4)**.

Interactions During Biotransformation

The process of conversion of drugs to their respective

metabolites is termed as *biotransformation* and it usually occurs in the liver **(Chap. 1.5)** These reactions are generally mediated by enzymes, so that drugs capable of altering the enzymatic processes involved in drug metabolism can lead to drug interactions.

Table 1.8-4. *Displacement of drugs from plasma protein binding sites*

Drug displaced (lower binding affinity)	*Displacing agent (higher binding affinity)*
Acetaminophen	Phenylbutazone, clofibrate, phenytoin, salicylates
Methotrexate	Salicylates, sulphonamides
Pamaquine	Quinacrine
Sulphonamides	Phenylbutazone, oxyphenbutazone, warfarin, salicylates, tolbutamide
Warfarin	Phenylbutazone, oxyphenbutazone, clofibrate, salicylates, phenytoin, sulphinpyrazone

Enzyme induction. Liver microsomal enzymes involved in drug motabolism can be stimulated by drugs including barbiturates, hydantoins, griseofulvin, chlorinated hydrocarbon insecticides and many others. This is termed as *enzyme induction* and results in a reduced therapeutic response to those drugs that are metabolized by microsomal enzymes **(Table 1.8-5)**.

Table 1.8-5. *Drugs that induce the metabolism of other drugs*

Inducer	*Drugs affected*
Alcohol	Tolbutamide
Chloral hydrate	Bishydroxycoumarin, warfarin
Chlorcyclizine	Steroid hormones
Haloperidol	Warfarin
Phenobarbital	Adriamycin, barbiturates, bishydroxycoumarin, chloramphenicol, cortisol, cyclophosphamide, digitoxin, griseofulvin, phenylbutazone, phenytoin, progesterone, testosterone, thyroxine, warfarin
Phenylbutazone	Steroid hormones
Phenytoin	Steroid hormones
DDT	Steroid hormones

Enzyme induction can be utilized for its beneficial effects also, *e.g., phenobarbitone* is used in the treatment of *neonatal hyperbilirubinaemia*, because it accelerates the metabolism of bilirubin to more readily excreted compounds. Further, enzyme induction may be responsible for development of *tolerance*, as some drugs stimulate their own liver metabolism, *e.g.*, phenobarbitone, meprobamate, orphenadrine, phenylbutazone.

Enzyme inhibition. Compounds that interfere with the activity of inactivating enzymes can potentiate the action of other drugs or endogenous substances, *e.g., monoamine oxidase inhibitors* (MAOIs) inhibit the normal functioning of the endogenous enzyme monoamine oxidase (MAO), elevate levels of biogenic amines and may produce a hypertensive crisis in the presence of pressor amines; *allopurinol*, xanthine oxidase inhibitor, increases plasma levels of mercaptopurine by blocking its breakdown; *physostigmine* and *neostigmine*, cholinesterase inhibitors, block the degradation of choline esters, and can enhance the effects of *acetylcholine*, other cholinergic drugs and *succinylcholine;* the anticonvulsant phenytoin is metabolized by hepatic microsomal enzymes, and its effects can be potentiated by microsomal enzyme inhibitors like *p-aminosalicylic acid, disulfiram, isoniazid* and *methylphenidate* due to accumulation of unmetabolized drug. These increased levels can result in toxicity **(Table 1.8-6)**.

Table 1.8-6 *Inhibition of drug metabolism*

Drug	*Metabolic inhibitor*
Bishydroxycoumarin	Chloramphenicol, oxypheanbutazone, phenylbutazone
Cyclophosphamide	Chloramphenicol
Hexobarbital	Metyrapone, p-aminosalicylate, norethynodrel, progesterone
6-Mercaptopurine	Allopurinol
Nortriptopurine	Allopurinol
Nortriptyline	Hydrocortisone
Pethidine	Oral contraceptives
Phenytoin	Bishdroxycoumarin, p-aminosalicylate, chloramphenicol, cycloserine, isoniazid, methylphenidate
Tolbutamide	Alcohol, chloramphenicol, phenylbutazone, monoamine oxidase inbhibitors, salicylates, probenecid

A therapeutically useful interaction based on enzyme inhibition is the combination of **carbidopa** with **levodopa.** Carbidopa competitively inhibits the enzyme dopa decarboxylase peripherally (outside the brain). This enzyme normally inactivates levodopa before it reaches its site of action in the brain. Thus, peripheral dopa decarboxylase inhibition permits a greater fraction of the dose of levodopa to enter the brain, leading to increased formation of dopamine to replace the deficient stores of dopamine and relieve symptoms of parkinsonism.

Interactions During Excretion

Interactions occuring during excretion of drugs may involve any of the renal excretory processes, *i.e.*, glomerular filtration, tubular reabsorption, or active tubular secretion. Most important drug interactions occur as a result of either *changes in urinary* pH which alters the fraction of reabsorbed drug, or through *competition for active tubular mechanisms.*

Changes in urinary pH. Acidification of the urine with agents like *ammonium chloride* results in reduced effectiveness of basic drugs (amphetamine, quindine), as they will be largely ionized in acidic pH and readily excreted. In contrast, renal excretion of acidic drugs (salicylates, barbiturates, anticoagulants) will be accelerated by alkalinization of urine with *sodium bicarbonate, acetazolamide* or *potassium citrate.* Thus, ammonium chloride may be given in amphetamine overdosage, whereas sodium bicarbonate may be used in phenobarbitone or salicylate overdosage.

Urinary pH also influences the solubility of drug molecules in tubular fluid, *e.g., sulphonamides* are poorly soluble in acidic urine and may precipitate in the renal tubules causing crystalluria and obstruction. Alkalinization of the urine facilitates the excretion of sulphonamides.

Competition for tubular mechanisms. Many drugs and metabolites are *actively* secreted from renal blood vessels into the tubules and subsequently eliminated. Interactions may occur when any *two actively secreted drugs are used together, due to competition for the active secretory mechanisms.* Drugs which may interact by this means, resulting in prolonged therepeutic effects are *salicylates, sulphonamides, penicillins, probenecid, thiazides, dicumarol, indomethacin, oral hypoglycaemics, acetazolamide, methotrexate* and *diazoxide.* Small doses of aspirin impair the uricosuric action of probenecid by interfering with the active secretion of uric acid into the renal tubules. Competition for active tubular secretion can be used therapeutically as well, *e.g.*, use of *probenecid* with *pencillin* to delay the rapid excretion of the penicillin molecule, leading to a significantly prolonged effective duration of action of penicillin.

Changes in fluid and electrolyte levels induced by certain drugs can affect the thereapeutic effectiveness and toxicity of other drugs, specially those acting on the heart, kidney and skeletal muscles. *Hypokalaemia* produced by diuretics and corticosteroids increases the likelihood of *digitalis toxicity,* and can *antagonize* the antiarrhythmic activity of quinidine, lidocaine, procainamide, phenytoin and disoyramide. Drugs that cause excessive diuresis (high-ceiling diuretics) may potentiate the hypotensive effects of antihypertensive drugs.

Pharmacodynamic Interactions

Pharmacodynamic interactions occur at the site of drug action. They usually lead to an altered sensitivity of the affected organ. Mostly drug effects are the result of binding of the drug to specialized areas on or within the cells, known as *receptor sites.* The magnitude of the effect depends on the *concentration of the free drug* at its receptor site. As already discussed in **Chapter 1.5**, the *free drug* or an active metabolite concentration at the receptor site depends on the amount of drug in the body, which in turn is regulated by: (*i*) physical and chemical properties of the drug; (*ii*) altered gastrointestinal absorption or competition for protein binding sites or receptor sites; (*iii*) altered drug metabolism; (*iv*) changes in acid–base equilibrium; and (*v*) alterations of haemodynamic or renal tubular function influencing renal drug clearance. The quantity of drug associated with receptor sites depends on the amount of drug in the body; its accessibility to the receptor; and the affinity constant of the drug for the receptor, *i.e.*, the ratio of association to dissociation constants of the drug for the receptor. Further details of drug–receptor interactions are covered in **Chapter 1.6**. Some basic and clinically important pharmacodynamic interactions may be considered under the following heads:

Interactions at adrenergic nerve terminals. These interactions may be at times severe and life threatening. They are of two major types : (*i*) those between monoamine oxidase inhibitors (MAOIs) and foodstuffs/drugs; and (*ii*) those between tricyclic antidepressants and catechlamines/ hypotensive drugs.

The MAOIs inhibit intraneuronal MAO, and the sensitivity to infused or injected indirectly acting sympathomimetics (amphetamines) is increased. Any foodstuff or beverage which contains significant amounts of tyramine may cause the release of accumulated noradrenaline from the adrenergic nerve terminals causing a hypertensive crisis. The substances which can interact with MAOIs are : *foodstuffs*—cheese, yoghurt, yeast extract, liver, broad beans; *beverages*—sherry, chianti, beer; and *drugs*—levodopa, tricyclic antidepressants.

Interactions in the CNS. The aminoglycoside antibiotics (streptomycin, kanamycin, gentamicin) and the potent loop diuretic frusemide when used concurrently may cause severe ototoxicity. The aminoglycosides also increase and prolong the action of skeletal muscle relaxants.

Interactions in the bronchial tree. Bronchial relaxation depends upon the formation of cyclic 3′5′-AMP (c-AMP). The formation of this "second messenger" is increased when adenylcyclase in stimulated by *catechlamines.* Alternatively, the breakdown of c-AMP can be inhibited by *aminophylline.* Thus the combination of the two may be useful in the treatment of bronchial asthma.

Receptor blockade. The development of drugs that selectively block receptors, particularly those of the automonic nervous system, has led to several important interactions, *e.g., alpha-adrenoceptor blockade* with phenoxybenzamine prevents the action of noradrenaline and other alpha-sympathomimetics; *beta-blockade* with proranolol reduces or abolishes the cardiac stimulating activity of adrenaline and isoprenaline. Antichlonergic action of tricyclic antidepressants and antihistamines reduces the effect of chlonergic drugs. Some important interactions at the receptor site are listed in **Table 1.8-7.**

Interactions in the heart. Interactions at this site mainly involve the *beta-adrenoceptor blockers* and *cardiac glycosides.* The beta-blockers can produce a profound bradycardia, and delayed auriculoventricular conduction. These actions are

Table 1.8-7. *Interactions occurring at receptor site.*

Drug A + Receptor ⟶ Drug A : Receptor complex ⟶ Response
Drug B + Receptor ⟶ Drug B : Receptor complex ⟶ No response (blockade)

Receptor/site	*A-type drugs*	*B-type drugs*
Vessel alpha receptor	Noradrenaline	Phentolamine, phenoxybenzamine, imipramine, phenothiazines
Vessel beta-receptor	Isoprenaline	Propranolol
Cardiac sino-atrial node	Acetylcholine	Atropine, antihistamines, imipramine, phenothiazines
Neuromuscular junction	Acetylcholine	d-Tubocurarine
Adrenergic neurone	Noradrenaline	Guanethidine, amphetamine, tricyclic antidepressants, phenothiazines
Liver cell	Vitamin K	Salicylates, propylthiouracil, anabolic steroids, chloramphenicol

mainly due to the unopposed action of the vagus nerve, and can be overcome by administering atropine concurrently.

The cardiotoxicity of *cardiac glycosides* increases to 3-fold by hypokalaemia induced by diuretics.

Adverse Drug Interactions

The number of potential drug interactions is large, but those which are more important involve drugs with a narrow margin between their therapeutic and toxic doses (low therapeutic index). Caution must be exercised whenever such drugs are prescribed concurrently with *digitalis glycosides, anticonvulsants, oral anticoagulants, oral hypoglycaemics, cytotoxic agents, hypotensives and MAOIs.* Some life-threatening interactions are listed in **Table 1.8-8.**

Table 1.8-8 *Some clinically observed adverse drug interactions*

Major Symptoms	*Interacting drugs*
Hypertensive crisis	MAOI + Tyramine (cheese) MAOI + methamphetamine
Haemorrhagic episodes	Warfarin + phenylbutazone Warfarin + sulphinpyrazone
Hypoglycaemic reaction	Tolbutamide + phenylbutazone Tolbutamide + sulfisoxazole
Cardiac arrhythmias	Digitalis + chlorothiazide Digitalis + reserpine
Respiratory paralysis	Neomycin + succinylcholine Neomycin + ether

Prevention of Adverse Drug Interactions

The truism "the harder you look, the more you find" is best exemplified in the area of drug interactions. Life-threatening emergencies like haemorrhage, hypoglycaemic coma, cardiac arrhythmias, convulsions or a hypertensive crisis may occur. It is important to recognize and prevent such catastrophies, for which certain guidelines would be helpful:

1. The more potent the drug, higher is the risk of toxicity.
2. When it is essential to use combinations of drugs that are highly protein bound, adjustment of dosage is required for proper and safe control.
3. Any drug that is lipid-soluble at physiological pH should be considered a candidate for its enzyme inducing capability, and the dosage should be appropriately adjusted.
4. Authentic manuals on drug interactions *must* be readily available for consultation.
5. Maintain a detailed drug history and medical record of the patient.
6. Avoid irrational polypharmacy.

Combinations of drugs are employed in therapy to enhance effects and to prevent adverse reactions. *Beneficial drug interactions* have a special place in the treatment of diseases, like *essential hypertention, tuberculosis* and *cancer.* Here mention must also be made about ***fixed-dose combination products*** available in the market. Some fixed-dose combinations are rational, *e.g.*, combination of a local anaesthetic with adrenaline to provide more effective and prolonged anaesthesia. However, the majority of *fixed-dose combinations* have certain ***disadvantages:*** (*i*) the dosage of individual ingredients cannot be adjusted to suit a particular patient; (*ii*) half-lives of individual agents may be different leading to accumulation of agents with longer half-lives on repeated dosing at a particular dose interval; (*iii*) there is a likelihood of some ingredients being administered unnecessarily to the patient; (*iv*) there is a possibility of increased toxicity and allergenicity without a corresponding increase in therapeutic efficacy; and (*v*) the higher cost of the product is to be borne by the patient.

There are, however, certain ***advantages*** of fixed-dose combinations, like: (*i*) the *synergistic* effect of aspirin with codeine for analgesia; and (*ii*) *improved compliance* by the patient, as the number of medicaments to be taken is reduced. Thus, certain rational fixed-dose combinations are useful, but the use of unnecessary and irrational combination products should be avoided.

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