Chapter 6 Adverse Drug Effects

Adverse effect is 'any undesirable or unintended consequence of drug administration'. It is a broad term, includes all kinds of noxious effect—trivial, serious or even fatal.

For the purposes of detecting and quantifying only those adverse effects of a drug which are of some import and occur in ordinary therapeutic setting, the term *adverse drug reaction* (ADR) has been defined as 'any noxious change which is suspected to be due to a drug, occurs at doses normally used in man, requires treatment or decrease in dose or indicates caution in the future use of the same drug'. This definition excludes trivial or expected side effects and poisonings or overdose.

Another term *'adverse drug event'* (ADE) has been used to mean 'any untoward medical occurrence that may present during treatment with a medicine, but which does not necessarily have a causal relationship with the treatment'. The idea is to record all adverse events first, and look for causality only while analyzing pooled data.

All drugs are capable of producing adverse effects, and whenever a drug is given a risk is taken. The magnitude of risk has to be considered along with the magnitude of expected therapeutic benefit in deciding whether to use or not to use a particular drug in a given patient, e.g. even risk of bone marrow depression may be justified in treating cancer, while mild drowsiness caused by an antihistaminic in treating common cold may be unacceptable.

Adverse effects may develop promptly or only after prolonged medication or even after stoppage of the drug. Adverse effects are not rare; an incidence of 10–25% has been documented in different clinical settings. They are more common with multiple drug therapy and in the elderly. Adverse effects have been classified in many ways. One may divide them into:

Predictable (Type A or Augmented) reactions (mechanism based adverse reactions) These are based on the pharmacological properties of the drug, which means that they are augmented, but qualitatively normal response to the drug; include side effects, toxic effects and consequences of drug withdrawal. They are more common, dose related and mostly preventable and reversible.

Unpredictable (Type B or Bizarre) reactions These are based on peculiarities of the patient and not on drug's known actions; include allergy and idiosyncrasy. They are less common, often non-dose related, generally more serious and require withdrawal of the drug. Some of these reactions can be predicted and prevented if their genetic basis is known and suitable test to characterize the individual's phenotype is performed.

Severity of adverse drug reactions has been graded as:

Minor: No therapy, antidote or prolongation of hospitalization is required.

Moderate: Requires change in drug therapy, specific treatment or prolongs hospital stay by at least one day.

Severe: Potentially life-threatening, causes permanent damage or requires intensive medical treatment.

Lethal: Directly or indirectly contributes to death of the patient.

Pharmacovigilance

Pharmacovigilance has been defined by the WHO (2002) as the 'science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems.' The information generated by pharmacovigilance is useful in educating doctors about ADRs and in the official regulation of drug use. Its main purpose is to reduce the risk of drug-related harm to the patient. It has an important role in the rational use of medicines, as it provides the basis for assessing safety of medicines.

The activities involved in pharmacovigilance are:

a. Postmarketing surveillance and other methods of ADR monitoring such as voluntary reporting by doctors (e.g. yellow card system of UK), prescription event monitoring, computerized medical record linkage and other cohort/case control studies as well as anecdotal case reports by doctors.

   Voluntary reporting depends on the initiative and willingness of the health professionals. It is minimal in India, while even in the developed countries only ~10% ADRs are reported voluntarily. Immediately occurring reactions and those that are dramatic are mostly reported. Though even rare reactions can be detected by this method, it does not provide incidence of the reaction.

b. Dissemination of ADR data through 'drug alerts', 'medical letters', advisories sent to doctors by pharmaceuticals and regulatory agencies (such as FDA in USA, committee on safety of medicines in UK).

c. Changes in the labelling of medicines indicating restrictions in use or statuary warnings, precautions, or even withdrawal of the drug, by the regulatory decision making authority.

Pharmacovigilance centres have been set up in most countries. The Uppsala Monitoring Centre (Sweden) is the international collaborating centre. In India, the Central Drugs Standard Control Organization (CDSCO) is coordinating the pharmacovigilance programme, under which peripheral, regional and zonal monitoring centres have been set up along with a National Pharmacovigilance advisory committee. The pharmacovigilance centres collect, communicate and disseminate ADR data by linking with hospitals as well as practitioners and are also expected to provide expertise for assessing causality and severity of ADRs by using standard algorithms and rating scales like the 'Naranjo algorithm' (causalilty assessment) and modified Hartwig scale (severity grading).

Causality assessment

When a patient undergoing drug therapy experiences an adverse event, it may be due to the drug, or the disease or some other causes. Most of the time, a clear-cut 'yes/no' cause and effect relationship between a drug and the adverse event cannot be pronounced. Causality is assessed on the basis of:

- *Temporal relationship:* How the time-sequence of the event is related to drug administration.
- *Previous knowledge:* Whether the drug is known to produce the event in earlier recipients with a certain degree of consistency.
- *Dechallenge:* Whether the event subsided on stopping the drug.
- *Rechallenge:* Whether the event reappeared when the drug was administered again after a gap during which the event had subsided. Many times rechallenge is unethical/dangerous, and is not done.

Assessed on the basis of the above criteria, causality has been graded as:

1. *Definite:* Causality is proven.
2. *Probable:* Though not proven, drug is the likely cause of the event.
3. *Possible:* Drug as well as other causes could be responsible for the event.
4. *Doubtful:* Drug unlikely to be the cause, but cannot be ruled out.

Prevention of adverse effects to drugs

Adverse drug effects can be minimized but not altogether eliminated by observing the following practices:

1. Avoid all inappropriate use of drugs in the context of patient's clinical condition.
2. Use appropriate dose, route and frequency of drug administration based on patient's specific variables.
3. Elicit and take into consideration previous history of drug reactions.

4. Elicit history of allergic diseases and exercise caution (drug allergy is more common in patients with allergic diseases).
5. Rule out possibility of drug interactions when more than one drug is prescribed.
6. Adopt correct drug administration technique (e.g. intravenous injection of vancomycin must be slow).
7. Carry out appropriate laboratory monitoring (e.g. prothrombin time with warfarin, serum drug levels with lithium).

Adverse drug effects may be categorized into:

1. Side effects

These are unwanted but often unavoidable pharmacodynamic effects that occur at therapeutic doses. Generally, they are not serious but may occasionally be hazardous, e.g. postural hypotension caused by prazosin as a side effect may result in fall and fracture neck femur in an elderly patient. Side effects can be predicted from the pharmacological profile of a drug and are known to occur in a given percentage of drug recipients. Reduction in dose, usually ameliorates the symptoms.

A side effect may be based on the same action as the therapeutic effect, e.g. atropine is used in preanaesthetic medication for its antisecretory action. The same action produces dryness of mouth as a side effect. Glyceryl trinitrate relieves angina pectoris by dilating peripheral vasculature which is also responsible for postural hypotension and throbbing headache.

The side effect may also be based on a different facet of action, e.g. promethazine produces sedation which is unrelated to its antiallergic action; estrogens cause nausea which is unrelated to their antiovulatory action.

An effect may be therapeutic in one context but side effect in another context, e.g. codeine used for cough produces constipation as a side effect, but the latter is its therapeutic effect in traveller's diarrhoea; depression of A-V conduction is the desired effect of digoxin in atrial fibrillation, but the same may be undesirable when it is used for CHF.

Many drugs have been developed from observation of side effects, e.g. early sulfonamides used as antibacterial were found to produce hypoglycaemia and acidosis as side effects which directed research resulting in the development of hypoglycaemic sulfonylureas and the carbonic anhydrase inhibitor—acetazolamide.

2. Secondary effects

These are indirect consequences of a primary action of the drug, e.g. suppression of bacterial flora by tetracyclines paves the way for superinfections; corticosteroids weaken host defence mechanisms so that latent tuberculosis gets activated.

3. Toxic effects

These are the result of excessive pharmacological action of the drug due to overdosage or prolonged use. Overdosage may be absolute (accidental, homicidal, suicidal) or relative (i.e. usual dose of gentamicin in presence of renal failure). The manifestations are predictable and dose related. They result from functional alteration (high dose of atropine causing delirium) or drug induced tissue damage (hepatic necrosis from paracetamol overdosage). The CNS, CVS, kidney, liver, lung, skin and blood forming organs are most commonly involved in drug toxicity.

Toxicity may result from extension of the therapeutic effect itself, e.g. coma by barbiturates, complete A-V block by digoxin, bleeding due to heparin.

Another action of the drug can also be responsible for toxicity, e.g.—

- Morphine (analgesic) causes respiratory failure in overdosage.
- Imipramine (antidepressant) overdose causes cardiac arrhythmia.
- Streptomycin (antitubercular) causes vestibular damage on prolonged use.

Poisoning In a broad sense, poisoning implies harmful effects of a chemical on a biological system. It may result from large doses of drugs because 'it is the dose which distinguishes a

drug from a poison'. *Poison* is a 'substance which endangers life by severely affecting one or more vital functions'. Poisons derived from biologic sources are also referred to as '*toxins*'. Not only drugs, but other household, environmental and industrial chemicals, insecticides, etc. are frequently involved in poisonings. Specific antidotes such as receptor antagonists, chelating agents or specific antibodies are available only for few poisons. General supportive and symptomatic treatment, as the need arises, is all that can be done for others, and this is also important for poisons which have a selective antagonist.

The general detoxification and supportive measures are:

1. *Resuscitation and maintenance of vital functions*

a. Ensure patent airway, adequate ventilation, give artificial respiration/100% oxygen inhalation as needed. This is important because severe poisoning often makes the patient comatose; protective airway reflexes and respiratory drive are lost.
b. Maintain blood pressure and heart beat by fluid and crystalloid infusion, pressor agents, cardiac stimulants, pacing, defibrillation, etc, as needed. Hypotension, often prolonged, is common in severe poisonings.
c. Prevent and manage seizures (with i.v. lorazepam).
d. Maintain body temperature.
e. Maintain blood sugar level by dextrose infusion, especially in patients with altered sensorium.

2. *Termination of exposure (decontamination)* Decontamination procedures should be started concurrently with the above supportive measures. It is done by removing the patient to fresh air (for inhaled poisons), removing contaminated clothing and washing the skin and eyes (for poisons entering from the surface), induction of emesis with syrup ipecac or gastric lavage (for ingested poisons). Emesis should not be attempted in comatose or haemodynamically unstable patient, as well as for kerosene poisoning due to risk of aspiration into lungs. These procedures are also contraindicated in corrosive and CNS stimulant poisoning. Emesis/gastric lavage is not recommended if the patient presents > 2 hours after ingesting the poison; if the poison/its dose ingested are known to be non-life-threatening, or if the patient has vomited after consuming the poison. Thus, induction of vomiting or gastric lavage is useful only in very few cases of poisoning.

3. *Prevention of absorption of ingested poisons* A suspension of 20–40 g (or 1g/ kg body weight) of activated charcoal, which has large surface area and can adsorb many chemicals, should be administered in 200 ml of water. However, strong acids and alkalies, metallic salts, iodine, cyanide, caustics, alcohol, hydrocarbons and other organic solvents are not adsorbed by charcoal. Charcoal should not be administered if there is paralytic ileus or intestinal obstruction or when the patient reports > 2 hours after ingesting the poison.

4. *Hastening elimination* of the poison by inducing diuresis (furosemide, mannitol) or altering urinary pH (alkalinization for acidic drugs, e.g. barbiturates, aspirin). However, excretion of many poisons, especially those which are eliminated mainly by hepatic metabolism, is not enhanced by forced diuresis and risk of fluid overload/electrolyte imbalance outweighs the benefit. This procedure is generally not employed now. Haemodialysis is more efficacious in hastening elimination of many drugs, including phenobarbitone, carbamazepine, valproate, lithium, salicylate, theophylline, etc.

4. Intolerance

It is the appearance of characteristic toxic effects of a drug in an individual at therapeutic doses. It is the converse of tolerance and indicates a low threshold of the individual to the action of a drug. Such subjects are individuals who fall on the extreme left side of the Gaussian

frequency distribution curve for sensitivity to the drug. Examples are:

- A single dose of trifluprομazine induces muscular dystonias in some individuals, specially children.
- Only few doses of carbamazepine may cause ataxia in some people.
- One tablet of chloroquine may cause vomiting and abdominal pain in an occasional patient.

5. Idiosyncrasy

Idiosyncrasy refers to genetically determined abnormal reactivity to a chemical. The drug interacts with some unique feature of the individual, not found in majority of subjects, and produces the uncharacteristic reaction. As such, the type of reaction is restricted to individuals with a particular genotype (*see* p. 76). In addition, certain bizarre drug effects due to peculiarities of an individual (for which no definite genotype has been described) are included among idiosyncratic reactions, e.g.:

- Barbiturates cause excitement and mental confusion in some individuals.
- Quinine/quinidine cause cramps, diarrhoea, purpura, asthma, angioedema of face and hypotension in some patients.
- Chloramphenicol produces nondose-related serious aplastic anaemia in rare individuals.

6. Drug allergy (hypersensitivity)

It is an immunologically mediated reaction producing stereotype symptoms which are unrelated to the pharmacodynamic profile of the drug. The symptoms may appear even with much smaller doses and have a different time course of onset and duration. This is also called *drug hypersensitivity*; but does not refer to increased response which is called supersensitivity. The target organs primarily affected in drug allergy are skin, airways, blood vessels, blood cells and gastrointestinal tract.

Allergic reactions occur only in a small proportion of the population exposed to the drug and cannot be produced in other individuals at any dose. Prior sensitization is needed and a latent period of at least 1–2 weeks is required after the first exposure. However, the sensitizing exposure may go unnoticed or may be environmental. The drug or its metabolite acts as an antigen (AG), or more commonly a *hapten* (incomplete antigen: drugs have small molecules which become antigenic only after binding with an endogenous protein) and induce production of antibody (AB)/sensitized lymphocytes. Presence of AB to a drug is not necessarily followed by allergy to it. Chemically related drugs often show cross sensitivity. A particular drug can produce different types of allergic reactions in different individuals, while widely different drugs can produce similar reaction. The course of drug allergy is variable; an individual previously sensitive to a drug may subsequently tolerate it without a reaction and *vice versa*.

Cardinal features of drug allergy

- Manifestations unrelated to the pharmacodynamic actions of the drug.
- Manifestations similar to food/protein allergy, allergic diseases.
- Severity of reaction poorly correlated with dose of the drug; even small dose may trigger severe reaction.
- Occur only in few recipients, cannot be produced in other individuals.
- Prior sensitization (known/unknown) is needed.
- Positive dechallenge (on withdrawal of drug) and rechallenge (even with small dose).

Mechanism and types of allergic reactions

A. Humoral

Type-I (anaphylactic) reactions Reaginic antibodies (IgE) are produced which get fixed to the mast cells and basophils. On exposure to the drug, AG: AB reaction takes place on the mast cell surface (*see* Fig. 11.2) releasing mediators like histamine, 5-HT, leukotrienes (especially LT-C4 and D4), prostaglandins, PAF, etc. resulting in urticaria, itching, angioedema, bronchospasm, rhinitis or anaphylactic shock. Anaphylaxis is usually heralded by paresthesia, flushing, swelling of lips, generalized itching,

wheezing, palpitation followed by syncope. The manifestations occur quickly (within minutes to few hours) after challenge and are called *immediate hypersensitivity*. Antihistaminic drugs are beneficial in some of these reactions.

Type-II (cytolytic) reactions Drug + component of a specific tissue cell act as AG. The resulting antibodies (IgG, IgM) bind to the target cells; on reexposure AG: AB reaction takes place on the surface of these cells, complement is activated and cytolysis occurs resulting in one or more of thrombocytopenia, agranulocytosis, aplastic anaemia, haemolysis, organ damage (liver, kidney, muscle), systemic lupus erythematosus.

Type-III (retarded, Arthus) reactions These are mediated by circulating antibodies (predominantly IgG, mopping AB). AG: AB complexes bind complement and precipitate on vascular endothelium and basement membrane in tissues, release chemotactic mediators and lytic enzymes giving rise to a destructive inflammatory response. Manifestations are rashes, serum sickness (fever, arthralgia, lymphadenopathy), polyarteritis nodosa, Stevens-Johnson syndrome (erythema multiforme, arthritis, nephritis, myocarditis, mental symptoms). The reaction develops in 3–4 days after exposure, and usually subsides in 1–2 weeks.

B. Cell mediated

Type-IV (delayed hypersensitivity) reactions These are mediated through production of sensitized T-lymphocytes carrying receptors for the AG. On contact with the AG these T cells produce *lymphokines* which attract granulocytes and generate an inflammatory response, causing contact dermatitis, certain types of rashes, fever, photosensitization. The reaction generally takes 2–3 days to develop.

Treatment of drug allergy

The offending drug must be immediately stopped. Most mild reactions (like skin rashes) subside by themselves and donot require specific treatment. Antihistamines (H_1) are beneficial in some type I reactions (itching, urticaria, rhinitis, swelling of lips, etc.) and some skin rashes (*see* p. 182). In case of anaphylactic shock or angioedema of larynx the resuscitation council of UK has recommended the following measures:

- Put the patient in reclining position, administer oxygen at high flow rate and perform cardiopulmonary resuscitation if required.
- Inject adrenaline 0.5 mg (0.5 ml of 1 in 1000 solution for adult, 0.3 ml for child 6-12 years and 0.15 ml for child upto 6 years) i.m.; repeat every 5–10 min in case patient does not improve or improvement is transient. This is the only life saving measure. Adrenaline should not be injected i.v. (can itself be fatal) unless shock is immediately life threatening. If adrenaline is to be injected i.v., it should be diluted to 1:10,000 or 1:100,000 and infused slowly with constant monitoring.
- Administer a H_1 antihistaminic (pheniramine 20–40 mg or chlorpheniramine 10–20 mg) i.m./slow i.v. It may have adjuvant value.
- Intravenous glucocorticoid (hydrocortisone sod. succinate 200 mg) should be added in severe/recurrent cases. It acts slowly, but is specially valuable for prolonged reactions and in asthmatics. It may be followed by oral prednisolone for 3 days.

Adrenaline followed by a short course of glucocorticoids is indicated for bronchospasm attending drug hypersensitivity. Glucocorticoids are the only drug effective in type II, type III and type IV reactions.

Drugs frequently causing allergic reactions

Penicillins	Aspirin
Cephalosporins	Indomethacin
Sulfonamides	Carbamazepine
Tetracyclines	Allopurinol
Quinolones	ACE inhibitors
Metronidazole	Methyldopa
Abacavir	Hydralazine
Antitubercular drugs	Local anaesthetics
Phenothiazines	

Skin tests (intradermal, patch) or intranasal tests may forewarn in case of Type I hypersensitivity, but not in case of other types. However, these tests are not entirely reliable—false positive and false negative results are not rare.

7. Photosensitivity

It is a cutaneous reaction resulting from drug induced sensitization of the skin to UV radiation. The reactions are of two types:

(a) Phototoxic Drug or its metabolite accumulates in the skin, absorbs light and undergoes a photochemical reaction followed by a photobiological reaction resulting in local tissue damage (sunburn-like), i.e. erythema, edema, vesicular eruption, blistering which have fast onset and shorter duration after exposure ends. This is followed by hyperpigmentation and desquamation. The lesions may be more severe with larger doses of the drug. The shorter wave lengths (290–320 nm, UV-B) are responsible. Drugs involved in acute phototoxic reactions are tetracyclines (especially demeclocycline) and tar products. Drugs causing chronic and low grade sensitization are nalidixic acid, fluoroquinolones, dapsone, sulfonamides, phenothiazines, thiazides, amiodarone. This type of reaction is more common than photoallergic reaction.

(b) Photoallergic Drug or its metabolite induces a cell mediated immune response which on exposure to light of longer wave lengths (320–400 nm, UV-A) produces a papular or eczematous contact dermatitis like picture that may persist long after exposure. Occasionally, antibodies may also mediate photoallergy and the reaction takes the form of immediate flare, itching and wheal on exposure to sun. Even small doses may trigger the reaction and lesions may extend beyond the exposed area. Drugs involved are sulfonamides, sulfonylureas, griseofulvin, chloroquine, chlorpromazine, carbamazepine.

Photosensitivity reactions can be prevented or minimized by avoidance of exposure to sun and effective use of topical sun screens (SPF 15–60; *see* Ch. 66). Local treatment of acute sun burn and blistering consists of soothing lotions (e.g. calamine lotion), wet dressings and mild topical steroids. Strong topical steroids are needed for photoallergy; severe cases may require systemic steroid therapy.

8. Drug dependence and drug addiction

Drugs capable of altering mood and feelings are liable to repetitive use to derive euphoria, recreation, withdrawal from reality, social adjustment, etc. Some subjects who take the drug repeatedly for personal gratification, progress in indulgence with the drug and start according higher priority to taking the drug than to other basic needs, often in the face of known risks to health. Many of these drugs also induce adaptive physiological changes which result in escalation of the dose needed to produce the same effect. Thus, '*tolerance*' develops and physiological equilibrium is disturbed when the drug is not present. Confusing terminology, *viz*'dependence', 'physical dependence', 'psychological dependence', 'addiction', 'habituation', 'drug abuse' has been used over the past to describe the above phenomena. The terms as understood and applied currently are briefly explained below.

Drug dependence It is an altered physiological state produced by repeated administration of a drug which necessitates the continued presence of the drug to maintain physiological equilibrium. Discontinuation of the drug results in a characteristic *withdrawal* (*abstinence*) *syndrome*. This has been earlier termed '*physical dependence*', but is now simply called 'dependence'. Since the essence of the process is adaptation of the nervous system to function normally in the presence of the drug, it has been also called '*neuroadaptation*'.

Drugs producing dependence are—opioids, barbiturates and other depressants including alcohol and benzodiazepines. Stimulant drugs, e.g. amphetamines, cocaine produce minimal or no dependence.

Drug addiction A person is said to have developed 'drug addiction' when he/she

believes that optimal state of well being is achieved only through the actions of the drug. The subject feels emotionally distressed if the drug is not taken. It often starts as liking for the drug effects and progresses to compulsive drug use in some individuals who lose control and cannot stop taking the drug, even if they known it to be harmful. This was earlier termed '*psychological dependence*'. However, to avoid confusion, the widely understood term '*drug addiction*' is used now.

Drug addiction is a pattern of compulsive drug use characterized by overwhelming involvement with the use of a drug. Procuring the drug and using it takes precedence over other activities. Even after withdrawal most addicts tend to relapse. Dependence, though a strong impetus for continued drug use, is not an essential feature of addiction. Amphetamines, cocaine, cannabis, LSD are drugs which produce addiction but little/no dependence. Moreover, drugs like nalorphine produce dependence without imparting addiction in the sense that there is little drug seeking behaviour.

Reinforcement It is the ability of the drug to produce effects that the user enjoys and which make him/her wish to take it again or to induce *drug seeking behaviour*. Certain drugs (opioids, cocaine) are strong reinforcers, while others (benzodiazepines) are weak reinforcers. Faster the drug acts, more reinforcing it is. Thus, inhaled drugs and those injected i.v. are highly reinforcing–produce an intense 'high' in dependent individuals.

Drug habituation This term has been used to denote less intensive involvement with the drug, so that its withdrawal produces only mild discomfort. Dependence is absent. Consumption of tea, coffee, tobacco, social drinking are regarded habituating but not addicting. Thus, the difference between addiction and habituation is only quantitative. It is difficult to delineate when 'desire' turns into 'craving'. As such, it is better to avoid using the term 'habituation' as a distinct phenomenon.

Drug abuse This is another frequently used term which refers to use of a drug by self medication in a manner and amount that deviates from the approved medical and social patterns in a given culture at a given time. The term conveys social disapproval of the manner and purpose of drug use. For regulatory agencies, *drug abuse* refers to any use of an ilicit drug.

The two major patterns of drug abuse are:

a. *Continuous use:* The drug is taken regularly, the subject wishes to continuously remain under the influence of the drug, e.g. opioids, alcohol, sedatives.
b. *Occasional use:* The drug is taken off-and-on to obtain pleasure or high, recreation (as in rave parties) or enhancement of sexual experience, e.g. cocaine, amphetamines, psychedelics, binge drinking (a pattern of excessive alcohol drinking), cannabis, solvents (inhalation), etc.

9. Drug withdrawal reactions

Apart from drugs that are usually recognised as producing dependence, sudden interruption of therapy with certain other drugs also results in adverse consequences, mostly in the form of worsening of the clinical condition for which the drug was being used, e.g.:

- Acute adrenal insufficiency may be precipitated by abrupt cessation of corticosteroid therapy.
- Severe hypertension, restlessness and sympathetic overactivity may occur shortly after discontinuing clonidine.
- Worsening of angina pectoris, precipitation of myocardial infarction may result from stoppage of β blockers.
- Frequency of seizures may increase on sudden withdrawal of an antiepileptic.

These manifestations are also due to adaptive changes, and can be minimized by gradual withdrawal.

10. Teratogenicity

It refers to the capacity of a drug to cause foetal abnormalities when administered to the pregnant mother. The placenta does not constitute a strict barrier, and any drug can cross it to a greater or lesser extent. The embryo is one of the most

Human teratogenic drugs

Drug	*Abnormality*
Thalidomide	phocomelia, multiple defects of internal organs
Anticancer drugs (methotrexate)	cleft palate, hydrocephalus, multiple defects, foetal death
Androgens	virilization; limb, esophageal, cardiac defects
Progestins	virilization of female foetus
Stilboestrol	vaginal carcinoma in teenage female offspring
Tetracyclines	discoloured and deformed teeth, retarded bone growth
Warfarin	depressed nose; eye and hand defects, growth retardation
Phenytoin	hypoplastic phalanges, cleft lip/palate, microcephaly
Phenobarbitone	various malformations
Carbamazepine	neural tube defects, assorted abnormalities
Valproate sod.	spina bifida and other neural tube defects, heart and limb abnormalities
Alcohol	low IQ baby, growth retardation, foetal alcohol syndrome
ACE inhibitors	hypoplasia of organs, growth retardation, foetal loss
Lithium	foetal goiter, cardiac and other abnormalities
Antithyroid drugs	foetal goiter and hypothyroidism
Indomethacin/aspirin	premature closure of ductus arteriosus
Isotretinoin	craniofacial, heart and CNS defects, hydrocephalus

dynamic biological systems and in contrast to adults, drug effects are often irreversible. The thalidomide disaster (1958–61) resulting in thousands of babies born with *phocomelia* (seal like limbs) and other defects focused attention onto this type of adverse effect.

In 1959 and subsequent couple of years, the incidence of a rare birth defect *phocomelia* (hands and feet arising almost directly from shoulders and pelvis, similar to flippers of a seal) shot up sharply in Europe. Other birth defects also increased considerably. Soon it was noticed that all mothers with malformed babies had taken a new sedative—anti-morning sickness drug *thalidomide* (which was marketed in 1957) during early pregnancy. Epidemiological studies confirmed that intake of thalidomide in the first trimester of pregnancy was responsible for the birth defects, and the drug was immediately banned worldwide. It has now been marketed again for restricted use as adjuvant in cancer chemotherapy.

Drugs can affect the foetus at 3 stages—

(i) *Fertilization and implantation*—conception to 17 days—failure of pregnancy which often goes unnoticed.

(ii) *Organogenesis*—18 to 55 days of gestation—most vulnerable period, deformities are produced.

(iii) *Growth and development*—56 days onwards — developmental and functional abnormalities can occur, e.g. ACE inhibitors can cause hypoplasia of organs, especially of lungs and kidneys; NSAIDs may induce premature closure of ductus arteriosus; androgens and progestins cause masculanization of female foetus, antithyroid drugs and lithium cause foetal goiter.

The type of malformation depends on the drug as well as the stage at which exposure to the teratogen occurred. Foetal exposure depends on the blood level and duration for which the drug remains in maternal circulation. The teratogenic potential of a drug is to be considered against the background of congenital abnormalities occurring spontaneously, which is ~ 2% of all pregnancies. Majority of implicated drugs are low grade teratogens, i.e. increase the incidence of malformations only slightly, which may be very difficult to detect, confirm or refute. Nevertheless, some drugs have been clearly associated with causing foetal abnormalities in human beings.

These are listed in the box on p.100. However, only few mothers out of all those who receive these drugs during the vulnerable period will get a deformed baby, but the exact risk posed by a drug is difficult to estimate.

The US-FDA has graded the documentation of risk for causing birth defects into five categories *viz.* A, B, C, D and X, indicating a range from A (safe) to X (contraindicated). Because evidence on teratogenic potential of drugs keeps accumulating, the FDA grading has become out-dated in many cases, and its utility is being questioned. The FDA is likely to change this grading system soon.

It is, therefore, wise to avoid all drugs during pregnancy, unless compelling reasons exist for their use, regardless of the assigned pregnancy category, or presumed safety (also *see* Appendix-2).

Frequency of spontaneous as well as drug induced malformations, especially neural tube defects, may be reduced by folate therapy during pregnancy.

11. Mutagenicity and Carcinogenicity

It refers to capacity of a drug to cause genetic defects and cancer respectively. Usually oxidation of the drug results in the production of reactive intermediates which affect genes and may cause structural changes in the chromosomes. Covalent interaction with DNA can modify it to induce mutations, which may manifest as heritable defects in the next generation. If the modified DNA sequences code for factors that regulate cell proliferation/growth, i.e. are protooncogenes, or for proteins that inhibit transcription of protooncogenes, a tumour (cancer) may be produced. Even without interacting directly with DNA, certain chemicals can promote malignant change in genetically damaged cells, resulting in carcinogenesis. Chemical carcinogenesis generally takes several (10–40) years to develop. Drugs implicated in these adverse effects are—anticancer drugs, radioisotopes, estrogens, tobacco. Generally, drugs which show mutagenic or carcinogenic potential are not approved for marketing/are withdrawn, unless they are useful in life-threatening conditions.

12. Drug induced diseases

These are also called *iatrogenic* (physician induced) diseases, and are functional disturbances (disease) caused by drugs which persist even after the offending drug has been withdrawn and largely eliminated, e.g.:

Peptic ulcer by NSAIDs and corticosteroids.
Parkinsonism by phenothiazines and other antipsychotics.
Hepatitis by isoniazid.
DLE by hydralazine.

☞ PROBLEM DIRECTED STUDY

6.1 A 40-year-man weighing 60 kg suffering from chronic cough with expectoration and fever was diagnosed to have cavitary pulmonary tuberculosis. He was put on the standard 1st line antitubercular regimen consisting of isoniazid (H) + rifampin (R) + pyrazinamide (Z) + ethambutol (E). His condition improved, but in the 4th week he developed jaundice with enlarged tender liver and rise in serum bilirubin as well as serum transaminase levels. He was suspected to have developed antitubercular drug induced hepatitis.

(a) Should his antitubercular treatment be stopped or continued?

(b) How would you proceed to confirm and identify the causative drug, and then select the alternative regimen?

(see Appendix-1 for solution)