4th Edition

Essentials of Pharmacology for Dentistry

Covering the latest curriculum

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CHAPTER 4

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.

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 reactions are based on pharmacological properties of the drug, i.e. they are augmented but qualitatively normal response to the drug. This type of adverse effects include side effects, toxic effects and consequences of drug withdrawal. They are more common, dose related and are mostly preventable and reversible.

Unpredictable (Type B or Bizarre) reactions These reactions are based on peculiarities of the patient and not on the drug's known actions. Such reactions 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 tests 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 or 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.

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. NSAIDs not to be given on empty stomach).
7. Carry out appropriate laboratory monitoring (e.g. prothrombin time with warfarin, serum drug levels with lithium).

The adverse drug effects may be categorized into:

1. Side effects

These are unwanted but often unavoidable pharmacodynamic effects that occur at therapeutic doses. Generally, side effects 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 the elderly patient. These 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, and the same produces dryness of mouth as a side effect; anti-inflammatory as well as gastric mucosal damaging effects of NSAIDs are due to inhibition of prostaglandin synthesis.

Side effect may also be based on a different facet of action, e.g. promethazine produces sedation which is unrelated to its antiallergic 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.

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. hypoglycaemia due to insulin, bleeding due to heparin.

Another action of the drug may be responsible for the toxicity, e.g.

- Morphine (analgesic) causes respiratory failure in overdosage.
- Gentamicin (antibacterial) in high dose causes vestibular damage.

Poisoning Poisoning 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 called '*toxins*'. Not only drugs but other household and industrial chemicals, insecticides, etc. are frequently involved in poisonings. Specific antidotes, such as receptor antagonists, chelating agents (for heavy metal poisoning) or specific antibodies are available only for a few poisons. General supportive and

symptomatic treatment 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.
b. Maintain blood pressure and heart beat by fluid and crystalloid infusion, pressor agents, cardiac stimulants, external cardiac massage or cardiac pacing, etc, as needed.
c. Maintain body temperature.
d. Maintain blood sugar level by dextrose infusion, especially in patients with altered sensorium.
e. Prevent and treat seizures by i.v. lorazepam injection.

2. Termination of exposure (decontamination) by removing the patient to fresh air (for inhaled poisons), 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. Emesis/gastric lavage is not recommended if the patient presents > 2 hours after ingesting the poison, or if the patient has vomited after consuming the poison.

3. Prevention of absorption of ingested poisons A suspension of 20–40 g (1 g/kg) 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.

4. Hastening elimination of the poison by inducing diuresis (furosemide, mannitol) or altering urinary pH (alkalinization for acidic drugs, e.g. barbiturates). However, excretion of many poisons is not enhanced by forced diuresis and this procedure is generally not employed now. Haemodialysis is more efficacious.

4. Intolerance

It is the appearance of characteristic toxic effects of a drug in an individual at therapeutic doses. Intolerance is the converse of tolerance, and indicates a low threshold of the individual to the action of a drug. These 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 triflupromazine induces muscular dystonias in some individuals, especially children.
- Only few doses of carbamazepine may cause ataxia in some people.
- One tablet of aspirin may cause gastric bleeding.

5. Idiosyncrasy

Idiosyncrasy refers to genetically determined abnormal reactivity to a chemical producing an uncharacteristic reaction. Certain adverse effects of some drugs are largely restricted to individuals with a particular genotype (*see* p. 63). 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.
- Chloramphenicol produces non-dose-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. This is also called *drug hypersensitivity*; but does not refer to increased response which is called supersensitivity.

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. The drug or its metabolite acts as antigen (AG) or more commonly hapten (incomplete antigen: drugs have small molecules which become antigenic only after binding with an endogenous protein) and induce production of antibody (AB) or sensitized lymphocytes. Presence of AB to a drug is not necessarily followed by allergy to it. Chemically related drugs often show cross sensitivity. One drug can produce different types of allergic reactions in different individuals, while widely different drugs can produce the same 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 are unrelated to the pharmacodynamic actions of the drug.
- Manifestations are similar to food/protein allergy, allergic diseases.
- Severity of reaction is 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. 7.2) 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 flushing, paresthesia, generalized itching, swelling of lips, wheezing, palpitation followed by syncope. The manifestations occur quickly (within minutes to few hours) after challenge and are called *immediate hypersensitivity*. This is the only type of allergic drug reaction that the dentist may have to treat himself.

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 usually develops in 3-4 days and 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 AG, these T cells produce lymphokines which attract granulocytes and generate an inflammatory response, producing contact dermatitis, some types of rashes, fever, photosensitization. The reaction generally takes > 12 hours to develop. *Dentists may develop contact dermatitis by repeated handling of local anaesthetics*; though this is now rare due to replacement of procaine by lidocaine and use of surgical gloves.

Treatment of Drug Allergy

The offending drug must be immediately stopped. Most mild reactions (like skin rashes) subside by themselves and do not require specific treatment. Antihistamines (H_1) are beneficial in some type I reactions (urticaria, rhinitis, swelling of lips, etc.) and some skin rashes.

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) i.m.; repeat every 5–10 min in case the 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 (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 especially valuable for prolonged reactions and in asthmatics.

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

Drugs frequently causing allergic reactions

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

Skin tests (intradermal injection, patch application) 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, blistering followed by hyperpigmentation and desquamation. The shorter wavelengths (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

wavelengths (320–400 nm, UV-A) produces a papular or eczematous contact dermatitis like picture. Occasionally, antibodies may also mediate photoallergy, and the reaction takes the form of immediate flare and wheal on exposure to sun. Drugs involved are sulfonamides, sulfonylureas, griseofulvin, chloroquine, chlorpromazine.

8. Drug dependence and drug addiction

Drugs capable of altering mood and feelings (mind altering effects) 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. They are said to be suffering from '*substance use disorder*'. 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 repreated 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 know 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 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.

Drugs can affect the foetus at three stages–

(i) *Fertilization and implantation*—conception to 17 days. This generally results in failure of pregnancy which goes unnoticed.
(ii) *Organogenesis*—18 to 55 days of gestation. This is the most vulnerable period, deformities are produced.
(iii) *Growth and development*—56 days onwards. Effect at this stage produces developmental and functional abnormalities, e.g. ACE inhibitors can cause hypoplasia of organs, especially of lungs and kidneys; NSAIDs may induce premature closure of ductus arteriosus; antithyroid drugs and lithium cause foetal goiter.

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, oesophageal, 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

The type of malformation depends on the drug as well as the stage at which exposure to the teratogen occurred.

The proven human teratogens are listed in the box above. 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.

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. Only emergency dental treatment should be undertaken during the most vulnerable period of organogenesis.

11. Carcinogenicity and mutagenicity

It refers to capacity of a drug to cause cancer and genetic defects respectively. Usually, oxidation of the drug results in the production of reactive intermediates which affect genes and may cause structural changes in the chromosomes. Chemical carcinogenesis is a well-recognized phenomenon but generally takes several (10–40) years to develop. Drugs implicated in these adverse effects are—anticancer drugs, radioisotopes, estrogens, tobacco.

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.

Essentials of Pharmacology for Dentistry

Essentials of Pharmacology for Dentistry provides core and contemporary pharmacological knowledge which specifically meets the needs of dental students and practicing dentists. It covers a broad range of topics from principles of drug action and drug handling by the body to systemic pharmacology, describing briefly various classes of drugs which act on different organ systems, highlighting their dental implications. Greater emphasis is placed on antimicrobials and other drugs which dentists actually use or prescribe to treat orodental conditions or to facilitate dental procedures. It makes them aware of orodental adverse effects of drug therapy, as well as the possibility of interactions with other drugs which the patient may be taking for concurrent medical conditions. A separate chapter covers drugs and aids specific for dental care, such as antiplaque drugs, anticaries drugs, desensitizing agents, dentifrices, etc. Another chapter outlines the first hand treatment of common medical emergencies that may arise during dental procedures, alongwith 'emergency drug tray' which must be available in ready-to-use condition in every dental office.

Highlights of the fourth edition

- Thoroughly revised and updated chapters, including recently introduced drugs.
- Eye catching hierarchical drug classification charts which help create pictorial memory.
- Several new figures, charts, tables and highlight boxes which illustrate and summarize important concepts/topics.
- Latest NACO guidelines for post-exposure prophylaxis (PEP) of HIV infection for healthcare workers.
- Systematized, user-friendly and improved lay-out.
- Full coverage of latest dental curriculum.

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