Factors modifying drug action

Variation in response to the same dose of a drug between different patients and even in the same patient on different occasions.
Differences among different individuals may arise due to:

Differences in pharmacokinetics / handling of the drug. This is more marked for drugs disposed by metabolism (e.g. Propranolol) than for drugs excreted unchanged (e.g. atenolol).

Variations in number or state of receptors, coupling proteins or other components of response.

Variations in neurogenic / hormonal tone.
A multitude of host and external factors influence drug response. They fall into 2 categories: Genetic and non-Genetic factors including environment.

The factors modify drug action either:

i. **Quantitatively** – Plasma concentration and / or the action of the drug is increased or decreased.

ii. **Qualitatively** – The type of response is altered e.g. drug allergy or idiosyncrasy.

The factors are

1. Body size

This influences the concentration of drug attained at the site of action. The average adult dose refers to individuals of medium built.
Doses calculation are therefore important for obese, lean and children.

Dose calculation based on weight

Individual Dose = BW (Kg) × Average adult dose divided by 70

Dose calculation based on Body surface area (BSA)

Individual Dose = BSA (M2) × Average adult dose divided by 1.7

BSA can be calculated using Dubois formula:

BSA (M2) = BW (Kg) 0.425 × Height (Cm) 0.725 × 0.007184

BSA dose recommendations are available mainly for anticancer agents and a few other agents.

2. Age

Children

The drug of a drug for children is often calculated from the adult dose.

Young's formula

Child dose = Age × Adult dose divided by (Age + 12)

Dilling's formula

Child Dose = Age × Adult dose divided by 20

Many manufacturers give dosage recommendations on mg/Kg basis.

Infants / children are not small adults. They have important physiological differences from adult. The newborn has low GFR and tubular transport is immature. Hepatic drug metabolizing mechanism is immature – chloramphenicol can produce gray baby syndrome.

BBB is more permeable – drugs attain higher concentration in the CNS (accumulation of bilirubin causes kernicterus).

Drug absorption may also be altered in infants because of lower gastric acidity and slower

intestinal transit.

Children are growing and are more susceptible to adverse drug reactions e.g. suppression of growth by corticosteroids.

Elderly
Renal function progressively declines (intact nephron loss); so that Gfr is ? 74% at 50 years and ? 50% at 75 years. Drug doses have to be reduced.

There is also a reduction of hepatic microsomal drug metabolizing activity and liver blood flow.

The elderly are prone to cumulative toxicity after prolonged drug administration.

Reduced drug absorption due to reduced blood flow to the intestines, less plasma protein binding, lower plasma albumin, reduced or increased volume of distribution.

Elderly are likely to be on multiple drug therapy e.g. for hypertension, diabetes, arthritis etc. which in turn increases chances of drug interactions.

Incidence of adverse drug reactions is much higher in the elderly.

3. Sex

Females have smaller body size and require doses that are on the lower side of the range.

In women consideration must be given to menstruation, pregnancy and lactation.

A number of hypertensives (clonidine, methyldopa, Beta Blockers, diuretics) interfere with sexual function.

Ketoconazole causes loss of libido in males but not in women.

Drugs used during pregnancy can affect the foetus.

4. Species and race

Differences in responsiveness to drugs among different species; rabbits are resistant to atropine, rats and mice are resistant to digitalis.
Among humans, some racial differences have been observed; Beta blockers are less effective as antihypertensives in Afro-Caribbeans, Indians tolerate thiacetone better than white.

5. Genetics

The dose of a drug to produce the same effect may vary by 4-6 fold among different individuals.

All key determinants of drug response, e.g. transporters, metabolizing enzymes, ion channels, receptors with their couplers are genetically controlled.

Pharmacogenetics – study of genetic basis for variability in drug response. It deals with genetic influences on drugs action and also drug handling by the body.

6. Psychological factor

Efficacy of a drug can be affected by patient's beliefs, attitudes and expectations.

This is particularly applicable to centrally acting drugs e.g. alcohol generally impairs performance but if punishment is introduced it may improve performance.

Placebo – use of an inert substance which is given in the garb of medicine. It works psychologically rather than pharmacologically and often produces results equivalent to an active drug. For example, treating a patient who in the opinion of the doctor does not require medication.

7. Pathological states

Several diseases can influence drug action.
? Gastrointestinal diseases
? These can alter absorption of orally absorbed drugs; drug absorption can increase or decrease.
? Liver diseases

First pass effect is decreased because of reduced liver metabolizing enzymes.

Serum albumin is reduced, therefore; there is reduced protein binding of acidic drugs; more of the drug available in free form.

Metabolism and elimination of some drugs (morphine, lidocaine, Propranolol) is decreased – their dose should be reduced.

Prodrugs that require hepatic metabolism for activation e.g. prednisone, bacampicillin are less effective and should be avoided.

Hepatotoxic drugs should be avoided in liver disease
? Kidney disease
It markedly affects pharmacokinetics of many drugs as well as alters the effects of some drug

Clearance of drugs that are primarily excreted unchanged (aminoglycosides, digoxin, phenobarbitone) is reduced in line with decrease in Creatinine clearance.

8. Tolerance

It refers to the requirement of a higher dose of a drug to produce a given response.
Loss of therapeutic efficiency (e.g. sulfonylureas in diabetes type 2).

Drug tolerance may be:

i. Natural
The species / individual is less sensitive to the drug; e.g. rabbits are tolerant to atropine.
Some individuals in any population are less responsive to drug action.

ii. Acquired
This occurs by repeated use of a drug in an individual who was initially responsive.
Body is capable of developing tolerance to most drugs especially the CNS depressants.
Uninterrupted presence of the drug in the body favours development of tolerance.

Tolerance need not develop to all actions of the drug e.g.

Tolerance occurs to the sedative action of phenobarbitone but not to its antiepileptic action.

Tolerance develops to the analgesic and euphoric action of morphine, but not as much to its constipating and miotic actions.

iii. Cross tolerance – The development of tolerance to pharmacologically related drugs, e.g. alcoholics are relatively tolerant to barbiturates and general anaesthetics.

9. Route of administration

Governs the intensity and speed of drug response.

Parenteral administration is often resorted to for more rapid, more pronounced action.

A drug may have entirely different uses through different routes.

10. Other drugs

Drugs can modify the response to each other by pharmacokinetic or pharmacodynamic interaction between them.

11. Cumulation

Any drug will accumulate in the body if the rate of administration is more than the rate of elimination.
Slowly eliminated drugs are particularly liable to cause cumulative toxicity e.g. prolonged use of chloroquine causes retinal damage.

12. Environmental factors and time of administration

Exposure to insecticides, carcinogens, tobacco smoke and charcoal broiled meat may induce drug metabolism.
Type of diet and temporal relation between drug ingestion and meals can alter drug absorption e.g. food interferes with drug absorption.
Hypnotics taken at night and in quiet, familiar surroundings may work more easily.