EDITORIAL

Drug Therapy: from Friend to Foe

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When a drug or medicinal preparation is prescribed and administered, the prescriber expects to achieve or witness a particular effect or effects in the recipient of the drug. These include: therapeutic, and for many drugs, also untoward effects. Therapeutic effect - **Friend** - is the desired outcome for which the drug is prescribed. Therapeutic effect may be: (a) Curative, i.e. to achieve a cure by sustained correction of the abnormality caused by the disease, e.g. pain of headache; or by removal of the cause, e.g. bacterial infection, (b) Palliative or symptomatic, to relieve the suffering (morbidity) before a cure is achieved e.g. fever and cough in chest infection; or when a cure cannot be achieved, e.g. hypertension, osteoarthritis., (c) Prophylactic or preventive: to prevent the complications of the disease, e.g. electrolyte imbalance in gastroenteritis, post-surgical infection; or untoward effects of the drug administered, e.g. gastric irritation caused by NSAIDs.

Untoward effects of a drug may be considered as those that are not therapeutic in nature as described above. There are many types of untoward effects; while some are unavoidable but well tolerated, others may be potentially or overtly harmful, in which case they are called “adverse drug reactions” - ADR - **Foe**. Untoward effects relevant to the present context include:

(1) Side-effect, which occurs with doses of the drug within therapeutic (recommended) range. It is caused by the drug acting on the unintended (non-diseased) sites. When a drug is administered systemically by any route of administration, it is carried via the blood stream and is distributed to many sites in the body; and some un-diseased organs and tissues may be vulnerable to drug’s action. In general, side-effects of the drug are unavoidable, the price to pay for the beneficial effects of the drug. Fortunately, at doses in the therapeutic range, side-effects are not always harmful, e.g. drowsiness caused by antihistamines, antipsychotics; transient loss of appetite or diarrhea during antibiotic therapy; flushing, tachycardia and thirst caused by anticholinergic agents etc. The offending drug should be discontinued only when the patient cannot tolerate its side-effects, or when there is unfavorable benefit versus risk ratio, i.e. when it becomes a **Foe**.

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(2) Toxicity, which is caused by an extension (augmentation) of either the therapeutic effect, e.g. antihypertensives, antidiabetics, sedatives; or by extension of side effects. It is due to the dose of the drug being in excess of therapeutic range. The "excess" here is relative rather than the absolute amount of the drug, since some individuals are overly (hyper-) sensitive to the drug's action, and the usual recommended dose is excessive for them. Toxicity implies a harmful or potentially harmful effect on the recipient of the drug, hence a **Foe**. Toxicity should be avoided if possible, e.g. by adjusting the dosage. However, there are some drugs which have a narrow "Therapeutic Index" - ratio between effective and toxic doses, in other words, a safety margin. When unavoidable, toxicity may be minimized by another drug or drugs if available, e.g. antacids, anti-emetics, anti-cholinergics for gastrointestinal disturbances caused by some anti-infective and anti-cancer drugs.

(3) Adverse Drug Reactions (ADR) implies that the drug effect is at least potentially harmful to the recipient. ADR may be due to Toxicity (above) or due to particular side-effects. They may also be due to direct injurious effect of the drug on body tissues, e.g. hepatotoxic, neurotoxic, ototoxic etc. Such direct injurious effects are usually dose-related, and may be synergistic between and among drugs, e.g. NSAIDs and corticosteroids on gastric mucosa, hepatotoxic drugs and alcohol on the liver, etc. In some cases, ADR may be minimized by adjustment of dosage, or by choosing alternative drugs which have similar therapeutic properties but less adverse effects on particular organs, especially in vulnerable patients, e.g. those in whom liver or kidney functions are compromised. Incidentally, allergy (of variable intensity) may also be considered as an ADR, confined to particular drugs and individuals.

Mechanisms of Drug Action

Drugs produce their pharmacological actions by causing changes in the cells, tissues, organs or biological systems of the body. The changes may be biochemical in nature, e.g. lowering of blood glucose or uric acid, change in pH and electrolyte composition of body fluids, acidity of gastric contents etc; or the change may be in the physical activity (increase or decrease) of cells, tissues or organs. Drugs produce these actions by virtue of their chemical nature (chemical reaction), by acting on specific receptors in tissues and enzymes, or by acting through chemical mediators, hormones, autacoids etc. In general, the magnitude of drug action is proportional to the amount (concentration) of drug present at the site(s) of action. A sufficient magnitude of action at the site would produce a discernible or clinical effect which may be biochemical or physical in nature. Therapeutic effect occurs when the drug renders the diseased entities to normal or as close to normal as possible, e.g. blood sugar/blood pressure in normal range, absence or

relief of pain, swelling, cough, diarrhoea etc. If the effect extends beyond normal range it becomes Toxicity, an ADR and **Foe**. As mentioned above, ADR may also be due to innate, direct injurious action of the drug.

Quantification of Drug Activity

First, the optimal therapeutic drug effect, e.g. eradication or inhibition of growth of a pathogen; specific biochemical change; change in activity of chemical transmitters etc., is defined. The concentration of the drug, and the dose to achieve this concentration to produce the therapeutic effect in 50% of cases, called the median inhibitory concentration - IC_{50} or median effective dose - ED_{50} is found out experimentally. The concentration of drug and the dose that will produce toxicity in 50% of cases, called the median toxic dose TD_{50} is also found out. The ratio of TD_{50} over ED_{50} represents the "Therapeutic Index" (TI) or safety margin of the drug. The higher the TI, the safer the drug, and vice versa. Now, the effective concentration of a drug that can be achieved by a particular dose can be calculated from pharmacokinetic parameters such as dose size (mg), bioavailability (F), the volume of distribution (Vd) and elimination half-life ($T_{1/2}$) of the drug. Theses parameters are usually available (in textbooks or drug pamphlets) for most of the drugs used clinically. Calculations are done according to the principles of Clinical Pharmacokinetics.

Drug Potency

It is a common assumption that potency of a drug is based on the dose size (amount) of drug required to produce a particular effect, that is, the smaller the dose, the more potent the drug, e.g. to relieve pain, decrease the blood pressure etc. According to the concept of Pharmacology, potency of a drug represents the maximum effect it can produce in a particular situation, e.g. relief of pain. Thus, paracetamol is considered of low analgesic potency since it can relieve only mild to moderate pain, whereas morphine is highly potent as it can relieve even the most severe pain, e.g. of malignancy or due to severe trauma.

Clinical Implications

From the above, the message is that a drug's therapeutic potency is definite and limited; and this is achieved at a particular concentration in the body, and its dose size is calculated to achieve it. Any concentration or dose higher than this would not increase the therapeutic effect but would lead to untoward effects, in particular, toxicity - hence counter-productive **(Foe)**. As mentioned above, the concentration of drug achieved by a particular dose can be calculated from pharmacokinetic parameters according to principles of Clinical Pharmacokinetics. If the median effective concentration IC_{50} or median

effective dose ED_{50} is known it can be compared with the actual concentration achieved (as calculated). Dosage adjustment can hence be made to achieve the desirable drug concentration for optimal therapeutic effect, and so prevent or minimize the toxic effects. In other words, preventing Drug Therapy to turn from **Friend** to **Foe**.