Posology and Dosage Regimen

Posology and dosage regimen:

- Posology: is the branch of medicine/pharmacy dealing with doses.

- Dose: is the quantitative amount administered or taken by a patient for the intended medicinal effect.

- The goal is to produce the optimum therapeutic effect in a particular patient with the lowest possible dose.

Factors affecting drug dosage:

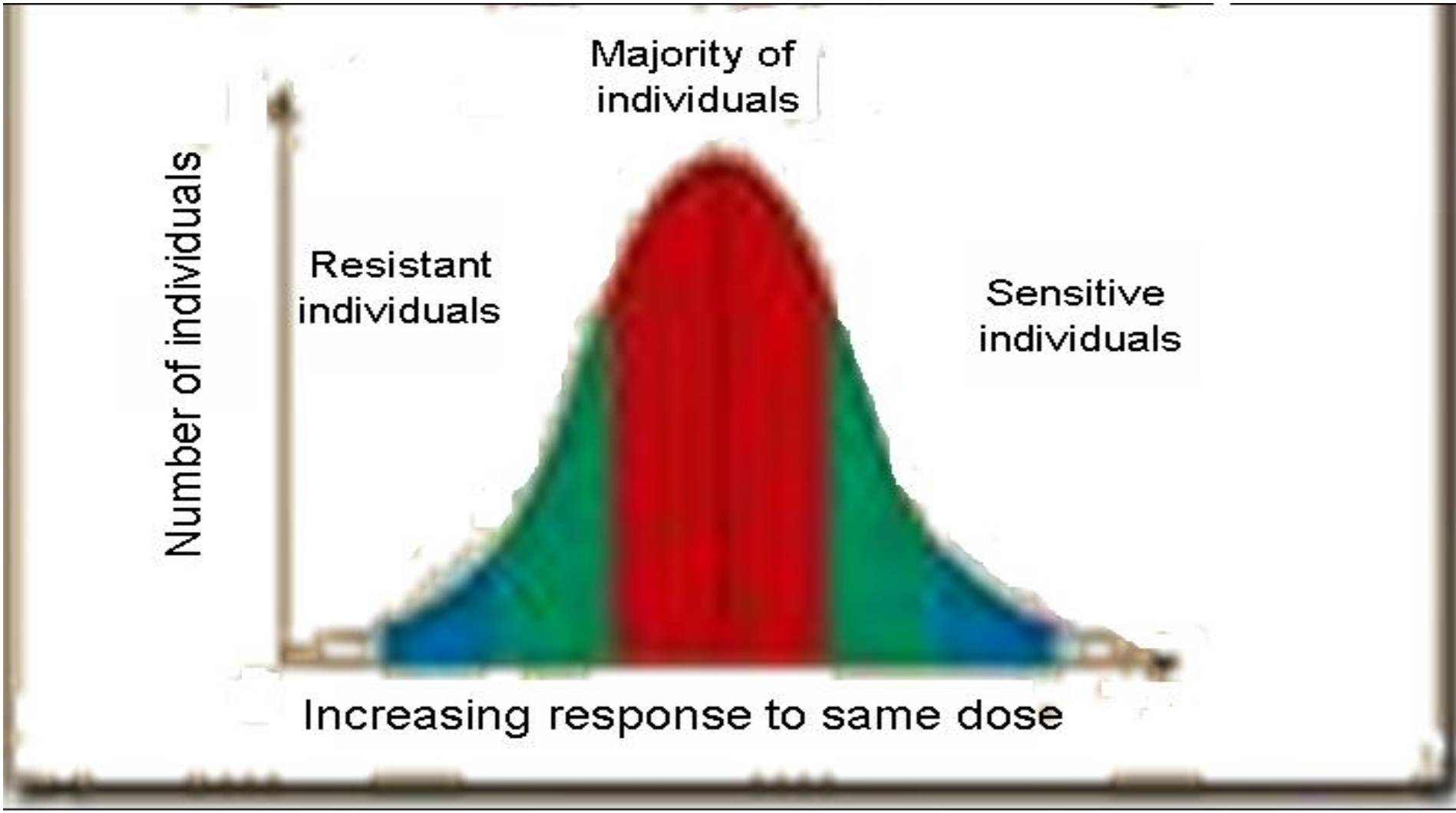
- The familiar bell-shaped curve shows that:

1- In a normal distribution of patients, a drug's usual dose will provide an average effect in the majority of individuals.

2- In a portion of the patients, the drug will produce little effect (resistant individuals).

3- In another group of similar size, the drug will produce an effect greater than the average effect (Sensitive individuals).

So, the drug's usual dose would be the starter dose for an individual taking the drug for the first time, then the physician may increase or decrease subsequent doses to meet the requirements of his patient.



Drug effect in a population sample (Dose – response curve)

Factors affecting drug dosage:

1- Age:

- Newborn infants (pediatric) are abnormally sensitive to certain drugs because of the immature state of their hepatic and renal function by which drugs are inactivated and eliminated from the body. Failure to detoxify and eliminate drugs results in their accumulation in the tissues to a toxic level.

- The decline in renal and hepatic function in the elderly (geriatric) may slow drug clearance and increases the possibility of drug accumulation in the body and subsequent toxicity. Elderly individuals may also respond abnormally to the usual amount of a drug because of changes in drug-receptor sensitivity or because of age-related alterations in target tissues and organs.

Factors affecting drug dosage:

<u>Various rules of dosage in which the pediatric dose was a fraction of the adult dose:</u>

based on age:

1. Young's rule

- For calculating doses for children two years of age or older.

$$\text{Dose for child} = \text{Adult dose} \times \frac{\text{Age}}{\text{Age} + 12}$$

Factors affecting drug dosage (Cont):

2- Cowling's Rule:

For calculating doses for children two years of age or older.

$$\text{Dose for child} = \text{Adult dose} \times \frac{\text{Age at next birthday (in years)}}{24}$$

3- Fried's Rule for infants:

For calculating doses for infants younger than one year of age.

$$\text{Dose for infant} = \text{Adult dose} \times \frac{\text{Age (in months)}}{150}$$

Factors affecting drug dosage:

2- Body weight:

- The official usual doses for drugs are considered suitable for 70 kg (150 pounds) individuals.

- The ratio between the amount of drug administered and the size of the body influences the drug concentration at the site of action. Therefore, drug dosage may require adjustment from the usual adult dose for abnormally lean or obese patients.

Factors affecting drug dosage:

To calculate the dose of a drug for children based on body weight:

The determination of drug dosage for children on the basis of body weight is more dependable than that based on age.

Clark's Rule:

$$\text{Dose for child} = \text{Adult dose} \times \frac{\text{Weight (in lb)}}{\text{150 (average weight of adult in lb)}}$$

Factors affecting drug dosage:

3- Body surface area:

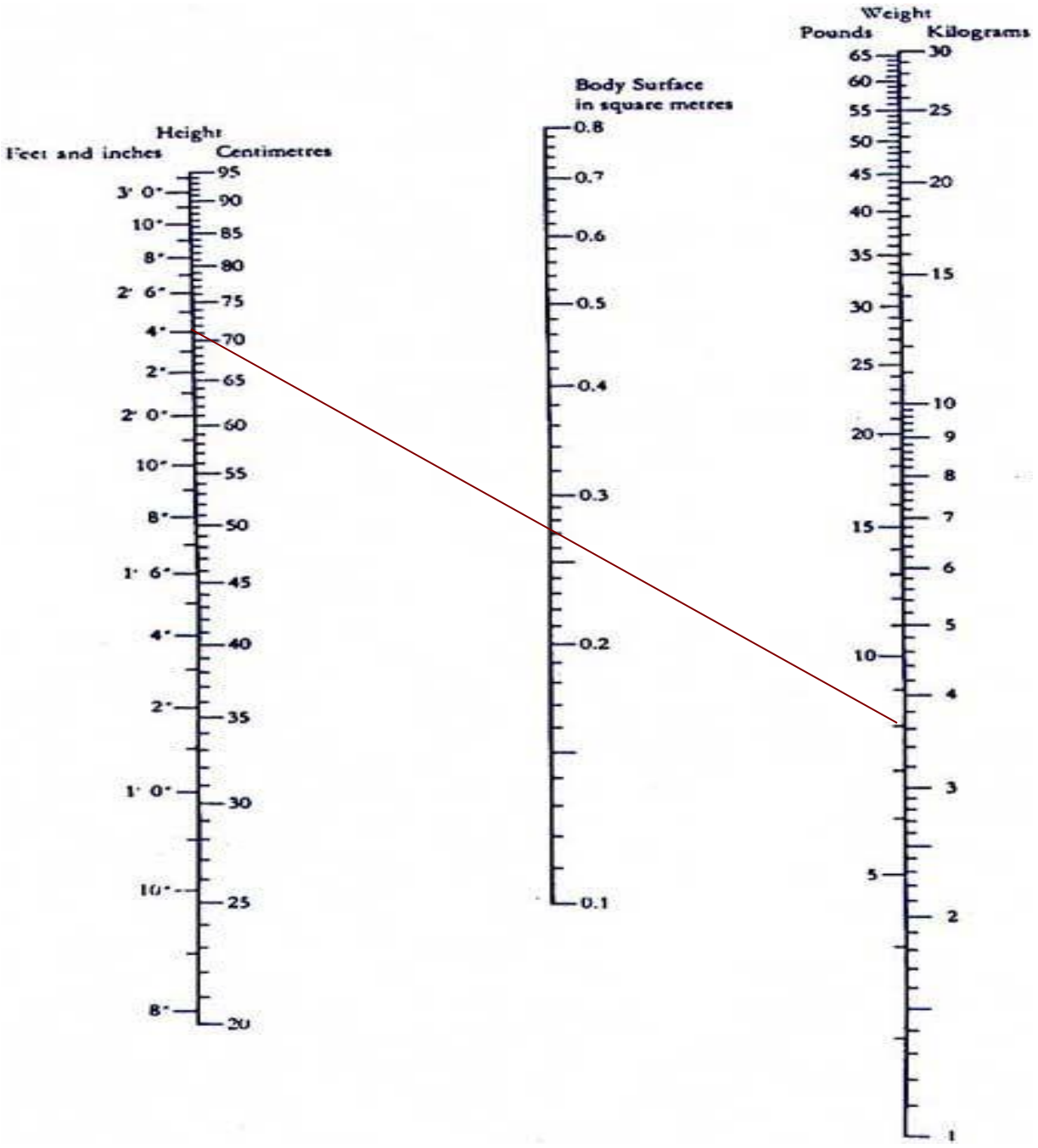
- A close relation exists between a large number of physiological processes and body surface area (BSA).

- The surface area of individuals may be determined from a nomogram composed of scales of height, weight and surface area.

- Two such nomograms are presented, one for adults and one for children.

- Surface area is indicated where a straight line drawn to connect the height and weight of an individual intersects the surface area column.

Nomogram


Height
Feet and inches
Centimetres
3' 0"
10"
8"
2' 6"
4"
2"
2' 0"
10"
8"
1' 6"
4"
2"
1' 0"
10"
8"
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
Body Surface
in square metres
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
Weight
Pounds
Kilograms
65
60
55
50
45
40
35
30
25
20
15
10
5
30
25
20
15
10
9
8
7
6
5
4
3
2
1

Factors affecting drug dosage:

To calculate the dose of a drug for children based on body surface area as related to weight:

Many physicians believe that doses for children should be based upon body surface area, since the correct dosage of drugs seems more proportional to the surface area.

$$\text{Approximate dose for child} = \text{Adult dose} \times \frac{\text{BSA of child (in } m^2\text{)}}{1.73\ m^2 \text{ (average adult BSA)}}$$

-If the dose per m2 is given,

Approximate dose for child = Dose per m2 x BSA of child (in m2)

Factors affecting drug dosage:

4-Sex:

- Women are more susceptible to the effects of certain drugs than are men.

- Pregnant women and nursing mothers should use medications only with the advise and under the guidance of their physician.

- Examples of drugs that are transported from the maternal to the fetal circulation e.g. alcohol, anesthetic gases, barbiturates, anticoagulants, etc.

- Because of the undeveloped drug detoxification and excretion mechanisms present in the fetus, concentrations of drugs may reach a higher level in the fetus than in the maternal circulation.

Factors affecting drug dosage:

- The transfer of drugs from the mother to the nursing infant through human milk may occur with various drugs with the drug effects becoming manifest in the infant.

5- Pathological state:

- The effects of certain drugs may be modified by the pathological condition of the patient and must be considered in determining the dose.
- Warning and precautions are used in the drug labeling to alert the physician to certain restrictions in the use of a particular drug.

Factors affecting drug dosage:

A- Precaution: Is used to advise the prescriber of some possible problems attendant with the use of the drug. It is less restrictive than warning.

e.g. The use of tetracycline antibiotic may result in overgrowth of fungi.

In such a case, the physician may prescribe an alternate drug.

B- Warning: It is used when the potential for patient harm is greater than in instances in which the precaution is used.

Factors affecting drug dosage:

e.g. If tetracycline is used in the presence of renal impairment, it may lead to accumulation of the drug and possible liver toxicity.

- Lower than usual doses are indicated.

- if therapy is prolonged, blood serum levels of the drug should be taken and the patient monitored at regular intervals to assure the maintenance of non-toxic levels of the drug.

C- Contraindication: A term that used to indicate an absolute prohibition to the use of a drug in the presence of certain stated conditions. It is the most restrictive of the warnings which limits the use of drugs.

Factors affecting drug dosage:

6- Tolerance:

Drug tolerance: The ability to endure the influence of a drug, particularly when acquired by a continued use of the substance.

- Tolerance occurs commonly in such drugs e.g. antihistaminics, narcotic analgesics.
- Normal sensitivity may be regained by suspending the drug administration for a period of time.
- The development of tolerance can be minimized by:

I. Initiating therapy with the lowest effective dose.

II. Avoiding prolonged administration.

Factors affecting drug dosage:

7- Drug-drug interactions:

- The effects of a drug may be modified by the concurrent administration of another drug.

- These drug-drug interactions are due to:

A- chemical or physical interaction between drugs.

B- alteration of the absorption, distribution, metabolism or excretion patterns of one of the drugs.

Factors affecting drug dosage:

The effects of drug-drug interactions may be:

I. Beneficial:

e.g. probenecid causes prolongation of penicillin serum levels (as it decreases its renal excretion). **So:**

- Reduction in penicillin dose is required.

- Decrease the frequency of its administration.

II. Detrimental:

- Many antacids drugs are rich in these metals should be:

• Avoided during tetracycline administration.

• Given alternately according to strict schedule.

e.g. diabetic patients who smoke heavily may require insulin dosage one-third higher than normal.

- Smoking – induced peripheral vasoconstriction reduces the rate of insulin absorption following subcutaneous absorption.

Factors affecting drug dosage:

8- Time of administration:

- The time at which a drug is administered sometimes influences dosage. This is specially true for oral therapy in relation to meals.

- Absorption proceeds more rapidly if the stomach and upper portions of the intestinal tract are free of food, and an amount of a drug that is effective when taken before a meal may be ineffective if administered during or after eating.

- Irritating drugs are better tolerated by the patient if food is present in the stomach to dilute the drug’s concentration.

Factors affecting drug dosage:

9- Route of administration:

- Drugs administered intravenously enter the blood stream directly and thus the full amount administered is present in the blood.
- In contrast, drugs administered orally are rarely fully absorbed due to the various physical, chemical and biologic barriers to their absorption, including interactions with the gastric and intestinal contents.
- Thus, a lesser parenteral dose of a drug is required than the oral dose to achieve the same blood levels of drug.

Factors affecting drug dosage:

10- Pharmaceutical dosage form and drug physical state:

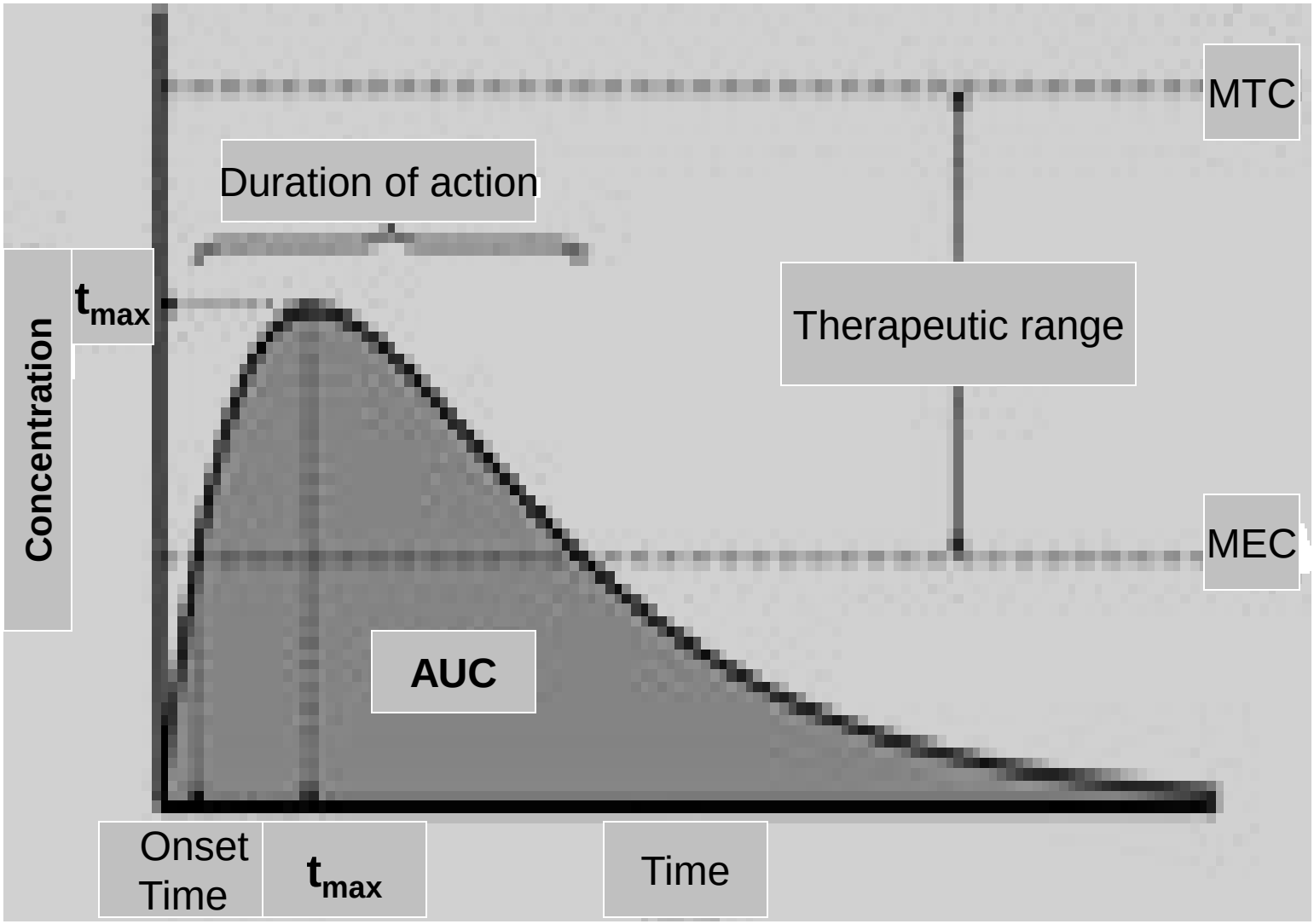
e.g. Increasing the surface area of a drug by the reduction of its particle size has a significant effect on the rate of absorption, therefore, the dose can be minimized by reducing the particle size.

- Thus, crystalline and amorphous forms of a drug shows a significant difference in the rate of absorption.

Dosage regimen:

- The schedule of dosing (e.g., four times a day for 10 days) is referred to as the **dosage regimen.**

- The proper selection of both the dose size and the frequency of administration is an important factor that influences whether a satisfactory therapeutic plasma concentration is achieved and maintained over the prescribed course of treatment.



A blood curve for a drug as a function of the time following oral administration.

Dosage regimen:

Definitions:

Minimum effective concentration (MEC): The minimum concentration that can be expected to produce the drug's desired effects in 50% of the individuals tested.

Minimum toxic concentration (MTC): The minimum concentration which produces toxic effects in 50% of the individuals tested.

Therapeutic index:

It is the ratio between a drug's minimum toxic dose and minimum effective dose ($TD_{50\%}$) / ($ED_{50\%}$).

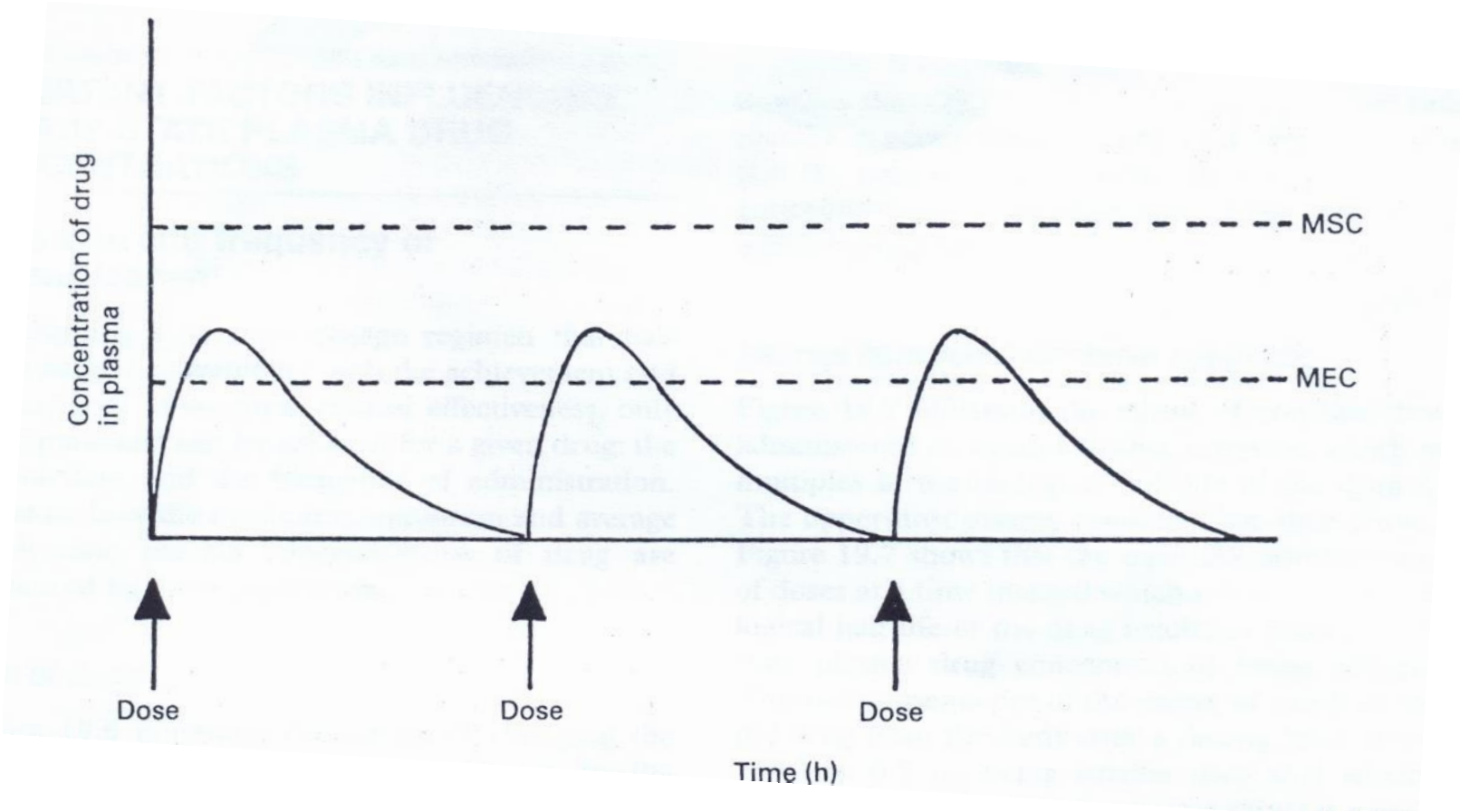
- ↑↑ therapeutic index is more favorable as it means that the drug is safe.
- Some drugs have low therapeutic index e.g. digoxin (TI = 2).

Dosage regimen:

How to design a satisfactory dosage regimen…..???

- The aim of drug therapy is to achieve a plasma concentration of drug which lies within the therapeutic range of that drug.

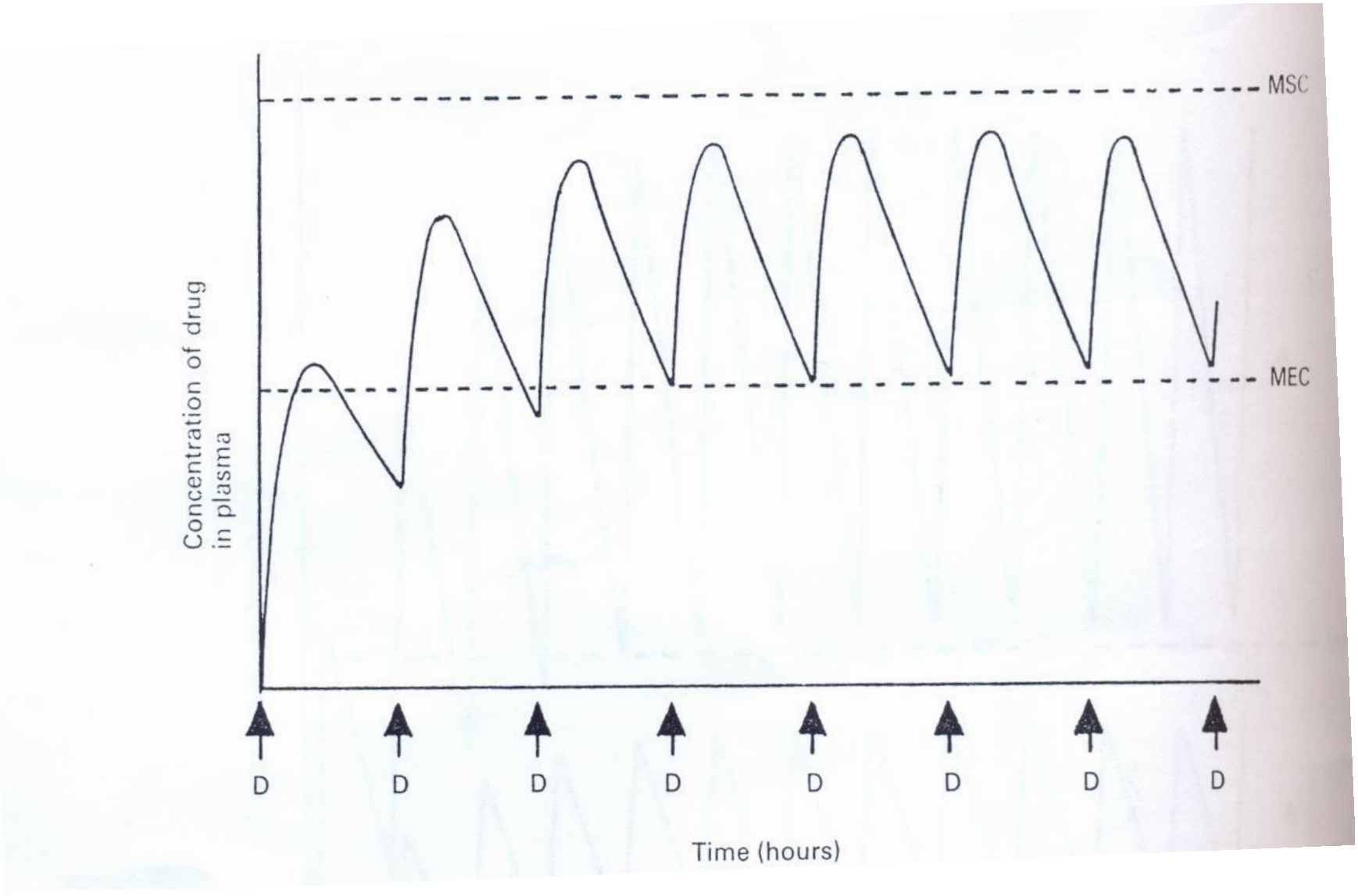
1- If the interval between each dose is longer than the time required for complete elimination of the previous dose, the plasma concentration-time profile of a drug will exhibit a series of isolated single-dose profiles. The design of this dosage regimen is unsatisfactory as the plasma concentration lies below the drug therapeutic range for long periods and so the patient will be under medicated (reduced or no therapeutic effect).



Plasma concentration-time curve following oral administration of equal doses of a drug at time intervals that allow complete elimination of the previous dose.

Dosage regimen:

2- If the dosing time interval is shorter than the time required for complete elimination of the previous dose, a steady state (drug concentration remains within therapeutic range) is reached which corresponds to the achievement and maintenance of maximal clinical effectiveness of the drug in the patient.



Plasma concentration-time curve following oral administration of equal doses of a drug. (a steady state is reached)

Dosage statements:

The usual dose of a drug:

The amount of the drug which may be expected to produce, in adults, the medicinal effect for which it was officially recognized.

The usual dosage range for a drug:

The quantitative range or amounts of the drug that may be prescribed within the framework of usual medical practice.

Doses falling outside of the usual dosage range may be either underdosage or overdosage.

Dosage statements:

The dosage regimen:

The schedule of dosage. It is indicated for those drugs that are best taken at specific intervals e.g. every 8 hours , e.g. at bedtime, e.g. before meals.

Initial,loading or priming dose:

It is a large single dose of the drug may be administered initially in order to achieve a peak plasma concentration that lies within the therapeutic range, which may then be maintained through the subsequent administration of regularly scheduled maintenance doses.

e.g. digoxin (cardiotonic agent)

Initially administered four or more times a day, followed by a single daily dose to maintain the desired blood level of the drug.

Dosage statements:

Maintenance doses:

Smaller, equal doses that administered at suitable fixed intervals to maintain the plasma concentrations of a drug.

Prophylactic doses:

doses that may be administered to protect the patient from contracting a specific disease, such as vaccines, baby Aspirin.

Therapeutic dose:

Which is administered to a patient after exposure or contraction of the illness.

Table 4.11. Factors That Determine a Dosage Regimen*

Activity-Toxicity	*Pharmacokinetics*
Minimum therapeutic dose	Absorption
Toxic dose	Distribution
Therapeutic index	Metabolism
Side effects	Excretion
Dose-response relationships	

Clinical Factors		*Other Factors*
Clinical State of Patient	*Management of Therapy*	
Age, weight, urine pH	Multiple drug therapy	Tolerance-dependence
Condition being treated	Convenience of regimen	Pharmacogenetics-idiosyncrasy
Existence of other disease states	Compliance of patient	Drug interactions

*Reprinted with permission from Rowland M, Tozer TN. Clinical Pharmacokinetics. 2nd Ed. Philadelphia: Lea & Febiger, 1989.