e-ISSN: 2248-9126
Vol3| Issue 2| 2013 | 79-89. Print ISSN: 2248-9118

Indian Journal of Pharmaceutical Science & Research

www.ijpsrjournal.com

A REVIEW ON DOSAGE REGIMEN

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ABSTRACT

Designing correct dose of drug for a particular patient is very important for proper therapeutic efficacy of drug and also it helps in the prevention of unwanted effects of drugs, there are several methods to design the dosage regimen which are clearly mentioned in this article, In this paper, I review studies in which compliance was measured to determine the associations between dose frequency and medication compliance.

Keywords: Dose frequency, dose regimen, steady state concentration.

INTRODUCTION

MULTIPLE DOSING

Dosage regimen is defined as the manner in which a drug is taken. For some drugs like analgesics, hypnotics, anti-emetics etc. A single dose is sufficient to provide effective treatment. In cases where illness is longer than the therapeutic effect produced by a single dose drugs should be taken repeatedly for a specific period of time. This is called as multiple dosage regimen. E.g.- Antibacterial, Anticonvulsants, Cardio tonics, Hormones [1].

OBJECTIVES OF MULTIPLE DOSING

- To prolong the therapeutic activity of the drug.
- To achieve maximum efficacy.

PARAMETERS TO BE ADJUSTED IN DEVELOPING A DOSAGE REGIMEN

1. Size of the drug dose.
2. Frequency of drug administration that is the time interval between the doses (T).
3. ajustement of both dose size & dose interval.

MULTIPLE IV BOLUS

After a single dose administration, we assume that there is no drug in the body before the drug is administrated and that no more is going to be administered. However, in the case of multiple dose administration we are expected to give second dosage and also subsequent doses before the drug is completely eliminated. Thus accumulation of drug of the drugs should be considered. On repeated drug administration, the plasma concentration will be added upon for each dose interval giving a plateau or steady state with the plasma concentration fluctuating between a minimum and a maximum [2].

If the doses are given far enough apart then the concentration will have fallen to approximately zero before the next dose. There will then be no accumulation of drug in the body.

ACCUMULATING DOSES

After administration of first dose Xo at $\tau=0$, the amount of drug in the body will be X=1Xo.

- At the next dosing interval when X=1/2Xo the amount of drug remaining in the body content to X=Xo +1/2Xo
- Accumulation occurs because drug from previous doses has not been removed completely.
- As the amount of drug in the body rises gradually due to accumulation.

When $\tau < t_{1/2}$, the degree of accumulation is greater and vice versa. Thus the extent to which a drug accumulates in the body during multiple dosing is a function of dosing interval and elimination half-life an is independent of dose size. The extent to which a drug will accumulate with any dosing interval in a patient can be derived from information obtained with a single dose and is given by accumulation index

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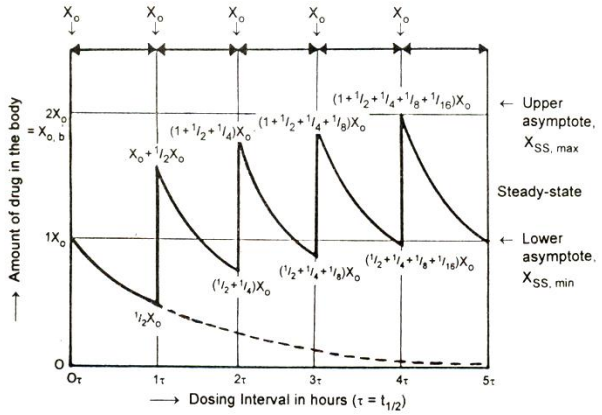


TIME TO REACH STEADY STATE DURING MULTIPLE DOSING

The time required to reach steady state depends primarily upon the half-life of the drug. Provided Ka >> K_E, the plateau principle is reached in approximately 5 half- lives. This is called as plateau principle. It also means that the rate at which the multiple dose steady-state is reached is determined only by K_E. The time taken to reach steady-state is independent of dose size, dosing interval and number of doses.

ACCUMULATION INDEX

The extent to which a drug will accumulate relative to the first dose can be quantified by an accumulation factor R.

The amounts of drug at steady sate are compared to the corresponding values at time t after the first dose i.e.

$$\frac{\text{Ass max}}{\text{Amax,1}} = \frac{\text{Ass, av}}{\text{Aav,1}} = \frac{\text{Ass min}}{\text{Amin,1}} = \frac{1}{1-e^{-k\tau}}$$

Therefore $R = \frac{1}{1-e^{-ke\,\tau}}$

R is an index of extent of accumulation

Also $R = \frac{1}{1-e^{-(0.693/\ t1/2)\,\tau}}$

R is dependent on the dosing interval τ and half-life.

AVERAGE AMOUNT OF DRUG AT STEADY STATE

The average drug concentration at steady state Css av is a function of maintenance dose Xo, the fraction of dose absorbed F, the dosing interval τ and clearance CL_T of drug.

Average rate in = Average rate out

Average rate in = $F \times \frac{\text{Dose}}{\tau}$

Average rate out = K. Ass av

Where Ass av is the average amount of drug in the body over dosing interval at plateau.

Therefore $F \times \frac{\text{Dose}}{\tau}$ = K. Ass av---------- (6)

$F \times \frac{\text{Dose}}{\tau}$ = K V Ass av ---------- (7)

$F \times \frac{\text{Dose}}{\tau}$ = CL Css av ---------- (8)

Where Css av = average plasma concentration at steady state.

$F \times \frac{\text{Dose}}{\tau} = \frac{0.693}{t_{1/2}}$ Ass av---------- (9)

Ass av = 1.44 F X Dose $t_{1/2}/\tau$ ---------- (10)

From equation 8 we can write the following equa for Css av.

$$\text{Css av} = \frac{F}{CL}\,\frac{\text{Dose (Xo)}}{\tau}$$

Thus the average amount of drug in the body at steady state depends on rate of administration, bioavailability and half-life and plasma drug concentration depends on also clearance apart from dose, bioavailability and dosing interval.

Average drug concentration can also be defined as

$$\text{Css av} = \frac{\text{AUC}}{\tau}$$

AUC is the area under the curve following a single maintenance dose.

LOADING AND MAINTENANCE DOSES

- A drug does not show therapeutic activity unless it reaches the desired steady- state.
- It takes about 5 half-lives to attain it and therefore the time taken will be too long if the drug has a long half-life.
- Plateau can be reached immediately by administering a dose that gives the desired steady-state instantaneously before the commencement of maintenance doses Xo.
- Such an initial or first dose intended to be therapeutic is called as primary dose or loading dose $Xo,_L$.

$$Xo,_L = \frac{\text{Css av}\ V_d}{F} \quad \text{---------- (1)}$$

- After e.v administration, Cmax is always smaller than that after iv administration and loading dose is proportionally smaller.
- When Vd is not known, loading dose may be calculated by following equation.

$$\frac{Xo,_L}{Xo} = \frac{1}{(1-e^{-k\,at})\ (1-e^{-ke\,\tau})}$$

The above equation applies when Ka>> K_E and drug is distributed rapidly. When the drug is given IV, the absorption phase is neglected and the above equation reduces to.

$$\frac{Xo,_L}{Xo} = \frac{1}{(1-e^{-ke\,\tau})} = \text{Rac}$$

$\frac{Xo,_L}{Xo}$ is called as dose ratio.

As a rule, when τ = t1/2 dose ratio should be equal to 2 but must be smaller than 2 when τ > t1/2 and greater when τ < t1/2. Fig shows that if loading dose is not

optimum, either too low or too high, the steady-state is attained within approximately 5 half-lives.

MULTIPLE ORAL DOSE ADMINISTRATION:

- Oral multiple dosing regimen is initiated plasma concentrations will increases, reach a maximum and begin to decline.
- A second dose will be administered before all of the absorbed drug from the first dose is eliminated.
- Plasma concentration resulting from the second dose will be higher than those from the first dose.
- This increase in concentration with dose will continue to occur until a steady state is reached at which the rate of drug entry into the body will equal the rate of exit.
- Hence the concentration at any time during a dosing interval should be the same from dose to dose.

Plasma concentration achieved following a single dose can be given by

$$\frac{C = F.\ Dose\ .\ Ka}{Vd\ (Ka-K)} [e^{-kt} - e^{-k\ at}] \quad \text{---------- (1)}$$

Ka is the absorption rate constant and
K is the elimination rate constant
During a multiple dose regimen for a constant dose and dose interval can be determined from the following equation.

$$\frac{C = F.\ Dose\ .\ Ka}{Vd\ (Ka-K)} \quad \frac{1- e^{-nk\tau}}{1- e^{-k\tau}} . e^{-kt} - \frac{1- e^{-k\tau}}{1- e^{-k\tau}} . e^{-kat} \quad \text{---------- (2)}$$

Where n = number of doses
τ = dosing inteval
t = time after administration of n doses
F = fraction of the dose absorbed
Equation 2 is a general equation.

There is accumulation of the drug in the body to some plasma concentrations fluctuate between a minimum and a maximum value.
The mean plasma level at steady state,

$$Css\ av = \frac{F.\ Dose}{Vd.\ K.\ \tau} \quad \text{---------- (3)}$$

Also

$$Css\ av = \frac{F.\ Dose}{CL\ .\ \tau} \quad \text{---------- (4)}$$

Css av can also be calculated from the equation

$$Css\ av = \frac{[AUC]^{\infty}_{0}}{\tau} \quad \text{---------- (5)}$$

where $[AUC]^{\infty}_{0}$ is the area under plasma concentration Vs time curve from t=0 to t=∞ following a single maintenance dose.
We get the same average plasma concentration whether the dose is given as a single dose every t dosing.
Eg: 300mg given every 12hr or 100mg every 4hr
At steady-state, the drug concentration at any time can be determined by letting n=∞. Therefore $e^{-nk\tau}$ becomes zero equation (2) can be written as

$$\frac{Css = F.\ Dose\ .\ Ka}{Vd\ (Ka-K)} \quad \frac{e^{-kt}}{1- e^{-k\tau}} - \frac{e^{-kat}}{1- e^{-ka\tau}} \quad \text{------- (6)}$$

If we assume that the subsequent doses are given after the plasma concentration has peaked $e^{-ka\tau} = 0$. That is the next dose is given after the absorption phase is complete.

Cmin at t = t is

$$\frac{Cmin = F.\ Dose\ .\ Ka}{Vd\ (Ka-K)} \quad \frac{e^{-kt}}{1- e^{-k\tau}} \quad \text{---------- (7)}$$

LOADING DOSE

Loading dose = maintenance dose / $1- e^{-k\tau}$ -------- (12)
From equation 3

Dm (maintenance dose) = Css,av Vd τ / 1.44 F $t_{1/2}$

Considering equation 8
Ka>> K then (Ka-K) is approximately equal to Ka and thus [Ka/ (Ka-K)] = 1
Therefore equation 8 can be written as

$$\frac{C^{ss}min = F.\ Dose\ .\ Ka}{Vd\ (Ka-K)} \quad \frac{e^{-kt}}{1- e^{-k\tau}} \quad \text{---------- (13)}$$

or $Cmin = Cmax\ e^{-kt}$ ---------- (14)

$$\frac{Cmax = Cmin}{e^{-kt}} \quad \text{---------- (15)}$$

INDIVIDUALIZATION
INTRODUCTION

Because of reasonable homogeneity in humans, the dosage regimens are calculated on population basis. However, same dose of a drug may produce large difference in pharmacological response in different individuals. This is called as intersubject variability. In other words, it means that the dose required to produce certain response varies from individual to individual. Rational drug therapy requires individualization of dosage regimen to fit a particular patient's needs. This requires knowledge of pharmacokinetics of drugs. The application of pharmacokinetic principles in the dosage regimen design for the safe and effective management of illness in individual patient is called as clinical pharmacokinetics.
The two sources of variability in drug responses are

1. **Pharmacokinetic variability** which is due to differences in drug concentrations at the site of action (as reflected from plasma drug concentration) because of inter individual differences in drug absorption, distribution, metabolism and excretion.
2. **Pharmacodynamic variability** which is attributed to differences in effects produced by a given drug concentration.

The major cause for variations is pharmacokinetic variability. Differences in the plasma levels of a given drug in the same subject when given on different occasions are called as intrasubject variability. It is rarely encountered in comparison to inter individual variations. The differences in variability differ for different drugs. Some drugs show greater variability than the others. The major causes of inter subject pharmacokinetic variability are genetics, disease, age, body weight and drug – drug interactions.

Less important causes are pharmaceutical formulations, route of administration, environmental factors and patient non-compliance.

The main objective of individualization is aimed at optimizing the dosage regimen. An inadequate therapeutic response calls for a higher dosage whereas drug related toxicity calls for a reduction in dosage. Thus in order to aid individualization, a drug must be made available in dosage forms of different dose strengths. The number of dose strengths in which a drug should be made available depends upon two major factors

1. The therapeutic index of the drug, and
2. The degree of inter subject variability. Smaller the therapeutic index and greater the variability, more the number of dose strengths required.

Based on the assumption that all patients required the same plasma drug concentration range for therapeutic effectiveness, the steps involved in the individualization of dosage regimen are

1. Estimation of pharmacokinetic parameters in individual patient and determining their deviation from the population values to evaluate the extent of variability; greater the accountability of variations better the chances of attaining the desired therapeutic objective.
2. Attributing the variability to some measurable characteristic such as: hepatic or renal disease, age, weight, etc.
3. designing the new dosage regimen from the collected data

The design of new dosage regimen involves

1. Adjustment of dosage, or
2. Adjustment of dosing interval, or adjustment of both dosage & dosing interval.

DOSING OF DRUGS IN OBESE PATIENTS

The apparent volume of distribution of a drug is greatly affected by changes in body weight since the latter directly related to the volume various body fluids. The ideal body weight (IBW) for men & women can be calculated from following formulae:

IBW (men) = 50kg ± 1kg /2.5 cm above or below 150 cm in height

IBW (women) = 45kg ±1kg /2.5 cm above or below 150 cm in height

Any person whose body weight is more than 25% above the IBW is considered obese. In such patients, the lean to adipose tissue ratio is small because of greater proportion of body fat, which alters the Vd of drugs. The ECF of adipose tissue is small in comparison to lean tissue in obese patients:

Following generalization can be made regarding drug distribution and dose adjustment in obese patients:

1. For drugs such as Digoxin that that do not significantly distribute in excess body space, the Vd do not change and hence dose to be administered should be calculated on IBW basis.
2. For polar drugs such as antibiotics (gentamicin) which distribute in excess body space of obese patients to an extent less than that in lean tissues, the dose should be lesser on per Kg total body weight basis but more than that on IBW basis.
3. In case of drugs such as caffeine, theophylline, lidocaine and lorazepam which distribute to the same extent in both lean and adipose tissues, the Vd is larger in obese patients but same on per Kg total body weight basis; hence, dose should be administered on total body weight basis.
4. For drugs such as a Phenytoin, diazepam and thiopental which are lipid soluble and distribute more in adipose tissues, the Vd is larger per Kg body weight in obese patients and hence they require larger doses, more than that on total body weight basis.

Changes in dose based on alteration of Vd is also attributed to modification of clearance and half-life of the drugs.

DOSING OF DRUGS IN NEONATES, INFANTS AND CHILDREN

The usual dosage regimen calculated on population bases refers to that for adults. Neonates, infants and children require different dosages than adults because of differences in body surface area, TBW and ECF on per Kg body weight basis. The dose for such patients are calculated on the basis of their body surface area and do not on body weight basis because the body surface area correlates better with dosage requirement, cardiac out put, renal blood flow and glomerular filtration in children. A simple formula in comparison to DuBois and DuBois for computing surface area (SA) in m^2 Mosteller's equation

$$\text{SA (in } m^2) = \frac{(\text{Height} \times \text{weight})^{1/2}}{60}$$

Infants & children require larger mg/kg doses than adults because:

1. their body surface area per Kg body weight is larger, and hence
2. larger volume of distribution (particularly TBW &ECF)

The child's maintenance dose can be calculated from adult dose by using the following equation:

$$\text{Child's Dose} = \frac{\text{SA of Child in } m^2}{1.73} \times \text{Adult dose}$$

Where 1.73 is the surface area in m2 of an average 70 kg adult. Since the surface area of a child is in proportion to the body weight according to the equation:

$\text{SA (in } m^2) = \text{Body weight (in Kg)}^{0.7}$

The following relationship can also be written for child's dose:

$$\text{Child's Dose} = \left[\frac{\text{Weight of child in Kg}}{70}\right]^{0.7} \times \text{Adult dose}$$

As the TBW in neonates is 30% more than that in adults,
1. the V_d for most water soluble is larger in infants, and
2. V_d for most lipid soluble is smaller,

Accordingly, the dose should be adjusted.

DOSING OF DRUGS IN ELDERLY PATIENTS

Drug dose should be reduced in elderly patients because of a general decline in body function with age. The lean body mass decreases and body fat increases by almost 100% in elderly persons as compared to adults. Because of smaller volume of body water, higher peak alcohol levels are observed in elderly subjects than in young adults. Vd of water soluble drug may decrease and that of a lipid soluble drug like diazepam increases with age. Age related changes in hepatic and renal function greatly alters the clearance of drugs. Because of progressive decrease in renal function, the dosage regimen of drugs that are predominantly excreted unchanged in urine should be reduced in elderly patients.

A general equation that allows the calculation of maintenance dose for a patient of any age (except neonates and infants) when maintenance of same Css.av is desired is:

$$\text{Patient's Dose} = \frac{(\text{Weight in Kg})^{0.7}\,(140 - \text{age in years})}{1660} \times \text{Adult dose}$$

DOSING OF DRUGS IN HEPATIC DISEASE

Disease is a major source of variations in drug response. Both pharmacokinetics and pharmacodynamics of many drugs are altered by diseases other than the one which is being treated.

The influence of hepatic disorder on drug availability and disposition is unpredictable because of the multiple effects that liver disease produces – effects on drug metabolizing enzymes, on drug binding and on hepatic blood flow. Hence, a correlation between altered drug pharmacokinetics and hepatic function is often difficult. For example, unlike excretion, there are numerous pathways by which a drug may be metabolized and each is affected to a different extent in hepatic disease. Generally speaking, drug dosage should be reduced in patients with hepatic dysfunction since clearance is reduced and availability is increased in such a situation.

DOSE ADJUSTMENT IN RENAL FAILURE

- Drug in patients with renal impairment have altered pharmacokinetic profile.
- Their renal clearance and elimination rate are reduced, the elimination half-life is increased and apparent volume of distribution altered.
- Since dose must be altered depending upon renal function in such patient.
- Except for drug having low therapeutic indices, the therapeutic range of others is sufficiently large and dose adjustment is not essential.
- The required dose in patient with renal impairment can be calculated by simple formula:-

Normal dose x RF

The dosing interval in hrs

$$\frac{\text{Normal interval in hrs}}{\text{RF}}$$

When the drug is eliminated both by renal and non-renal mechanisms, the dose to be administered in patients with renal failure is obtained from Normal dose (RF x Fraction excreted in urine + Fraction eliminated non-renally).

There are two additional methods for dose adjustment in renal insufficiency if the Vd change is assumed to be negligible. These methods are based on maintaining the same average steady-state concentration during renal dysfunction as that achieved with the usual multiple dosage regimen and normal renal function.

Dose adjustment based on total body clearance

The parameters to be adjusted in renal insufficiency are shown below:

$Css.av = F \times 1/Cl_T \times X_0/\tau$

Css.av – to be kept normal

F – Assumed constant

$1/Cl_T$ – decreased due to disease

X_0/τ – needs adjustment

If Cl_T' X_0' and τ' represent the values for the renal failure patient, then the equation for dose adjustment is given as:

$Css.av = X_0 /Cl_T \tau = X_0' / Cl_T' \tau'$

Rearranging in terms of dose and dose interval to be adjusted, the equation is:

$X_0' / \tau' = Cl_T' X_0 / Cl_T \tau$

From the above equation, the regimen may be adjusted by reduction in dosage or increasing in dosing interval or a combination of both.

Dose adjustment based on elimination rate constant or half-life

The parameters to be adjusted in renal insufficiency are:

$Css.av = 1.44F / Vd \times t_{1/2} \times X_0/\tau$

Css.av – to be kept normal

1.44F / Vd – assumed constant

$t_{1/2}$ – increased due to disease

X_0/τ – needs adjustment

If $t_{1/2}'$, X_0' and τ' represent the values for the renal failure patient, then the equation for dose adjustment is given as:

$Css.av = t_{1/2} X_0 /\tau = t_{1/2}' X_0' / \tau'$

Rearranging in terms of dose and dose interval to be adjusted, the equation is:

$X_0' / \tau' = t_{1/2} X_0 / t_{1/2}' \tau$

Because of prolongation of half-life of drug due to reduction in renal function, the time taken to achieve the desired plateau takes longer the more severe the

dysfunction. Hence, such patients sometimes need loading dose.

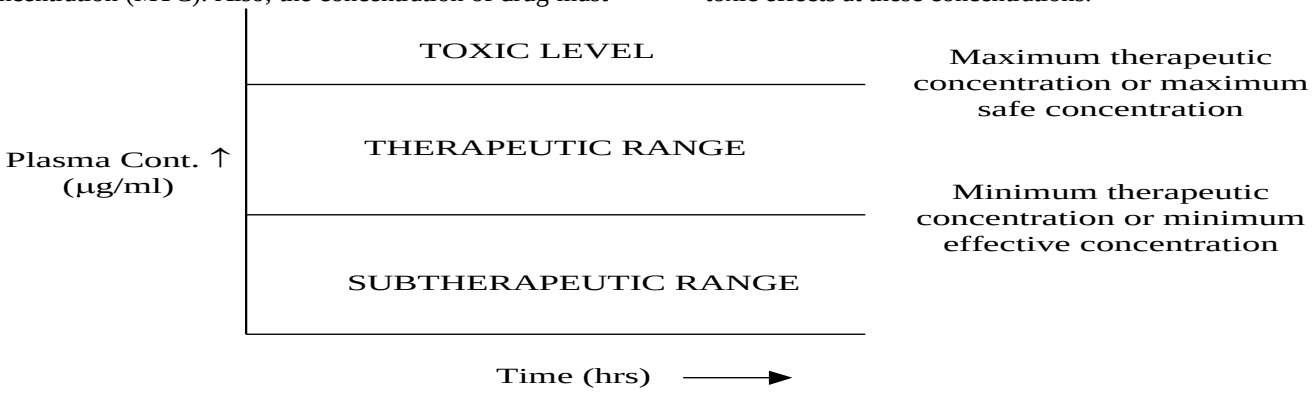
THERAPEUTIC DRUG MONITORING

Therapeutic drug monitoring involves monitoring, concentration of drug in plasma for optimal drug therapy i.e. it involves determination of concentration of drug in the plasma to optimize a patient's drug therapy. The primary objective of TDM is to attain rapid and safe concentration of drug in plasma within the desired therapeutic range in order to provide the safest approach to optimal drug therapy.

The usefulness of plasma drug concentration data in pharmacokinetic (PK) studies is based on the concept that pharmacologic response of a drug is closely related to concentration of drug at the receptor site (or site of action). Therefore, the concentration of drug at the site of action must attain a certain minimum level before the drug can elicit its therapeutic response. This minimum level of concentration has been termed as minimum effective concentration (MEC) or minimum therapeutic concentration (MTC). Also, the concentration of drug must be maintained below a certain level, termed minimum toxic concentration (MTC) or maximum safe concentration (MSC). It is expected that within this concentration range the drug will exhibit its therapeutic activity.

Since it is difficult, if not impossible to measure concentration of drug at the specific receptor site or site of action and because concentration of drug in the plasma appears to correlate the concentration of drug at the site of action, one determines concentration of drug in the plasma as a measure of concentration of drug at the site of action.

The pharmacokinetic data generated for a drug are usually based on studies conducted on a large patient population. These studies provide information on the range of plasma concentration that is effective and safe in treating specific disease conditions. Within this range, termed the therapeutic range, the drug exhibits its desired effects, but below this range, called the sub-therapeutic range, the therapeutic effects are not seen. Plasma concentration above the therapeutic range is generally termed as the toxic levels because the drug may exhibit toxic effects at these concentrations.



Since a large population is used in determining therapeutic and toxic concentrations of the drug, the data obtained reflect an average or mean value for these concentrations.

Individual patient response often plays an important role in the determination of therapeutic and toxic concentration of drug in the plasma.

In most scientific studies, large differences have been reported in individual patient response to treatment with a given drug. Therefore, the reported average values of therapeutic and toxic concentration of a drug are usually accompanied within a wide range. Hence there may be substantial overlap in the values of these concentrations, that is, the therapeutic concentration of a drug in one individual may prove to be sub-therapeutic concentration in another individual and toxic concentration in somebody else.

Therefore it should be realized that there is no fine line of demarcation which separates subtherapeutic, therapeutic and toxic concentration of a given drug and these concentration are not necessarily divided by absolute boundaries.

Definition: Management of drug therapy in individual patient often requires evaluation of response of the patient to the recommended dosage regimen. This is known as monitoring of drug therapy. It is necessary to ensure that the therapeutic objective is being attained and failure to do so requires readjustment of dosage regimen.

Candidates for Therapeutic Drug Monitoring or Necessity of Therapeutic Drug Monitoring:

All drugs and dosage forms are not good candidates for therapeutic drug monitoring. Drugs and dosage forms that lend themselves to TDM must possess specific characteristics. Drugs that are currently subjected to therapeutic monitoring have at least the following characteristics.

- Drugs with narrow therapeutic index.
- Small change in concentration may lead to a large change in drug response.

- Drugs showing poor and erratic absorption.
- Drugs showing marked inter individual variability.
- Highly potent drugs.
- Drugs whose signs of toxicity are difficult to recognize clinically.
- Drugs prescribed during renal or hepatic failure.
- Patients on multiple drug therapy showing interactions [3].

Therapeutic Monitoring for Many Drugs may not be necessary

This is due to the following reasons:-

1) Some drugs have a broad range of effective and safe dosage regimens.
2) For some drugs it is not necessary to determine plasma concentration, because more effective and less expensive intermediate measures of response are available to determine whether the dose of the drug should be increased, reduced or no change in dose is necessary. For ex. measurement of blood pressure in therapy with drugs that affect blood pressure, blood coagulation time with anticoagulants, absence of seizures in antiepileptic therapy are good indicators of therapeutic dose of the drug.
3) Some drugs have such a narrow range of flexibility in their dosage that the relationship between plasma concentration of drug and its clinical response is not firmly established.
4) Therapeutic drug monitoring is as expensive proposition. It is costly in terms of equipments used in monitoring drug therapy. Supplies needed for such monitoring and investment needed for the collection of necessary data which can be used to correlate the concentration of drug in plasma versus response from the drug dose.

Criteria for valid TDM

TDM can produce its desired results only with the cooperation of patient, and the medical team i.e. physician, pharmacist and nursing staff. The validity of TDM depends on;

1) Whether the patient is following the prescription promptly.
2) Whether he is complying with dietary restrictions if any.
3) Whether desired effects are being observed with the prescribed dosage or any readjustment is needed.
4) Whether any side effects, adverse effects are reported with therapy besides the ones usually mentioned with the drugs.
5) Whether incompatibility and wrong prescriptions have been checked.

A sound knowledge of pharmacokinetics (ADME) is very much essential during TDM. This would help in monitoring any impaired absorption in prescribed patients ex. The absorption of drugs may get impaired if the patient who is getting a treatment for a particular disease develops diarrhoea with excess gastrointestinal motility wherein the drug can get eliminated quickly resulting in impaired absorption and improper serum levels. Similarly observing its distribution levels, its metabolic pattern, as in case of impaired liver function or cardiac output, determine the concentration. The pharmacokinetic pattern needs to be readjusted for the validity of TDM [4].

Organization of a TDM Service

The TDM service requires the team work of pharmacologist, biochemist, apart from the clinical team. Whether the clinician feels the necessity of TDM for a patient, he can request for the same by providing the following information. The following information is required by TDM service provider which would serve as a document of rational therapy:

1) Name and address of patient
2) Age, weight, Sex
3) History of idiosyncraqcy (if any)
4) Disease diagnosed as
5) Details of treatment he/she is undergoing
6) Patient history for allergies or about previous medications
7) Time and data of administration
8) Duration of stay at hospital
9) Functional status of organs like liver, kidney, presently or any previous reports regarding him.
10) Reasons for TDM

a) Poor response for drugs
b) Toxicity observed
c) Any other

TDM service is effective, valuable and essential beyond doubt and is an effective tool in optimizing the therapy. It also ensures a rational therapy by suggesting an follow up therapy or stoppage or readjustments in dosage depending on the need. The total concept of TDM helps in individualizing the treatment.

The functions of TDM service are as given below.

1) Select drug
2) Design dosage regimen
3) Evaluate patient response
4) Determine need for measuring serum drug concentration
5) Assay for drug
6) Pharmacokinetic evaluation of drug levels
7) Readjust dosage regimen
8) Monitor serum drug concentration
9) Recommend special requirements

Due to interpatient variability in drug absorption, distribution and elimination as well as changing pathophysiologic conditions in the patient, therapeutic drug monitoring (TDM) or clinical pharmacokinetic (Laboratory) services (CPKS) have been established in many hospitals to evaluate the response of the patient to the recommended dosage regimen. The improvement in the

clinical effectiveness of the drug by therapeutic drug monitoring may decrease the cost of medical care by preventing untoward adverse drug effects. The functions of TDM service are given below.

1) Drug Selection

Physician usually chooses the drug and drug therapy. However many physicians consult with the clinical pharmacist in drug product selection and dosage regimen design. Increasingly, clinical pharmacists in hospitals and nursing care facilities are closely involved in prescribing, monitoring and substitution of medications. Drugs are selected not only on the basis of therapeutic consideration but also on the basis on cost and therapeutic equivalence. Pharmacokinetics and pharmacodynamics are part of the overall considerations in the selection of a drug for inclusion into the drug formulary (DF).

2) Dosage Regimen Design

Once the proper drug is selected for the patient, a number of factors must be considered when designing a therapeutic dosage regimen:-

a) Pharmacokinetics of the drug (ADME Profile)
b) Physiology of the patient (age, weight, gender)
c) Pathophysiologic conditions (renal dysfunction, hepatic disease, congestive heart failure)
d) Personal life style factors (cigarette smoking, alcohol abuse).

3) Pharmacokinetics of the drug

The pharmacokinetic parameters such as clearance, bioavailability, elimination half-life are valuable in clinical situations. Ideally the target drug concentration and the therapeutic widow for the drug should be obtained, if available. In using the target drug concentration in the development of a dosage regimen, the clinical pharmacist should know whether the reported target (effective) drug concentration represents an average steady state drug concentration, a peak drug concentration or a trough concentration.

4) Drug Dosage Form

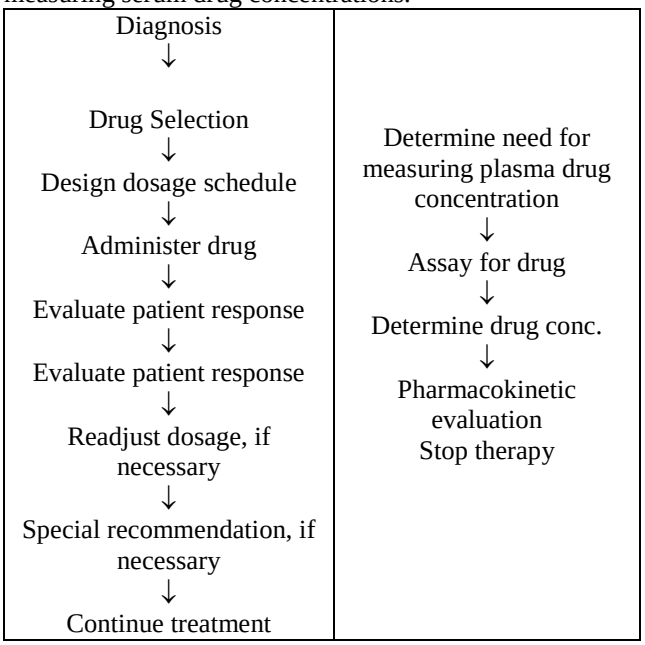
The drug dosage form will affect the bioavailability of the drug and thus the subsequent pharamcodynamics of the drug in the patient. The route of drug administration and the desired onset and duration of the clinical response will affect the choice of the drug dosage form.

5) Patient Compliance

Institutionalized patients may have very little choice as to the prescribed drug and drug dosage form. Moreover patient compliance is dictated by the fact that medication is provided by the medical personnel. Ambulatory patients must remember to take the medication as prescribed to obtain the optimum clinical effect of the drug. Factors that may effect patient compliance include cost of the medication, complicated instructions, multiple daily doses, difficulty in swallowing and adverse drug reactions. Therefore it is very important that the clinician or clinical pharmacist consider the patient's life style and needs when developing a drug dosage regimen.

6) Evaluation of Patient's Response

After a drug product is chosen and the patient receives the initial dosage regimen the practitioner should clinically evaluate the patient's response. If the patient is not responding to drug therapy as expected, then the drug and dosage regimen should be reviewed. The dosage regimen should be reviewed for adequacy, accuracy and patient compliance to the drug therapy. In many situations, sound clinical judgment may preclude the need for measuring serum drug concentrations.



Steps involved in the process of reaching dosage decisions with therapeutic drug monitoring.

7) Measurement of Serum Drug Concentrations

Before blood samples are taken from the patient, the practitioner needs to determine whether serum drug concentrations should be measured in the patient. In some cases, the patient's response may not be related to the serum drug concentration. for example, allergy or mild nausea may not be dose related.

The serum drug concentrations relate to the therapeutic and/or toxic effects of the drug knowledge of serum drug concentration may clarify why a patient is not responding to the drug therapy or why they drug is having an adverse effect. In addition, the practitioner may want to verify the accuracy of the dosage regimen.

When ordering serum drug concentrations to be measured, a single serum drug concentration may not yield

useful information unless other factors are considered. For example, the dosage regimen of the drug should be known, including the size of the dose and dosage interval, the route of drug administration, the time of sampling (peak, trough or steady state) and the type of drug product (e.g. immediate release or extended release).

8) Assay for Drug

Drug analyses are usually performed by either a clinical chemistry laboratory or a clinical pharmacokinetics laboratory. A variety of analytical techniques are available for drug measurement including HPLC, gas chromatography, spectrophotometry, fluorometry, immunoassay and radioisotopic methods. The methods used by the analytic laboratory may depend on such factors as the physicochemical characteristics of the drug, target concentration for measurement, amount and nature of the biological specimen (serum, urine), available instrumentation, cost for each assay and analytical skills of the laboratory personnel.

9) Pharmacokinetic Evaluation

After the serum drug concentrations are measured, the pharmacokineticist must properly evaluate the data. The assay results from the laboratory may show that the patient's serum levels are higher, lower or similar to the expected serum levels. The pharmacokineticist should evaluate these results while considering the patient and the patient's pathophysiologic condition.

10) Dosage Adjustment

From the serum drug concentration data and patient observations, the clinician or pharmacokineticist may recommend an adjustment in dosage regimen. Ideally the new dosage regimen should be calculated using the pharmacokinetic parameters derived from the patient's serum drug concentrations. Although there may not be enough data for a complete pharmacokinetic profile, the pharmacokineticist should still be able to derive a new dosage regimen based on the available data and the pharmacokinetic parameters in the literature that are based on average population data.

11) Monitoring Serum Drug Concentrations

In many cases, the patient's pathophysiology may be unstable, either improving or further deteriorating. For example, proper therapy for congestive heart failure will improve cardiac output and renal perfusion, thereby increasing renal drug clearance. Therefore continuous monitoring of serum drug concentration is necessary to ensure proper drug therapy for the patient. For some drugs an acute pharmacologic response can be monitored in lieu of actual serum drug concentration. For ex. Prothrombin clotting time might be useful for monitoring anticoagulant therapy and blood pressure monitoring for hypotensive agents.

12) Special Recommendations

At times, the patient may not be responding to drug therapy due to other factors. For ex. The patient may not be following instructions for taking the medication (patient non-compliance) may be taking the drug after a meal instead of before, or may not be adhering to a special diet (e.g. low salt). Therefore, the patient may need special instructions that are simple and easy to follow.

13) Design of Dosage Regimens

Several methods may be used to design a dosage regimen. Generally, the initial dosage of the drug is estimated using average population pharmacokinetic parameters as obtained from the literature. The patient is then monitored for the therapeutic response by physical diagnosis and if necessary, by measurement of serum drug levels. After evaluation of the patient, a readjustment of the dosage regimen may be indicates, with further therapeutic drug monitoring.

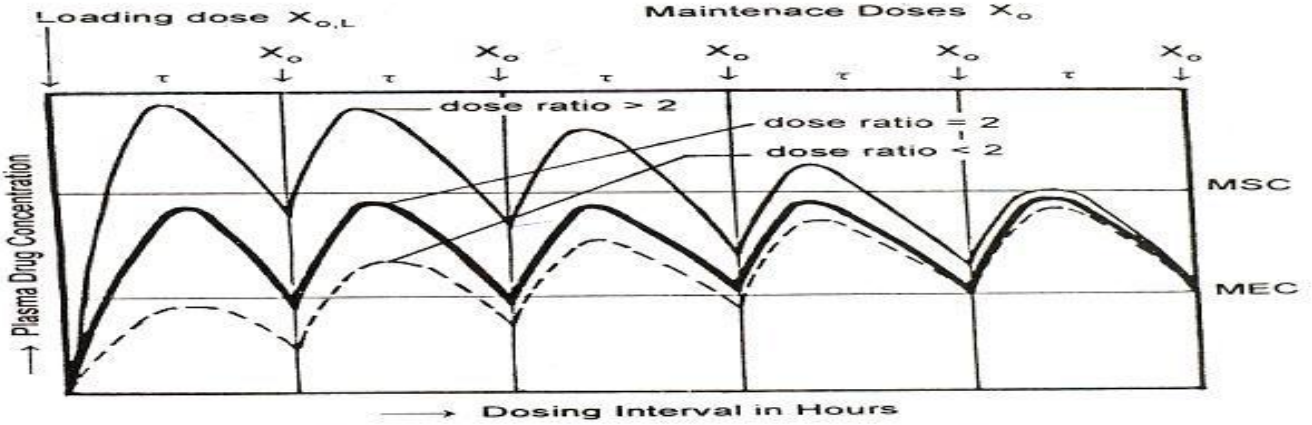


Fig. 13.4 Schematic representation of plasma concentration-time profiles that result when dose ratio is greater than 2.0, equal to 2.0 and smaller than 2.0.

TDM SERVICE LABORATORY

Name: Age: ___ years

Address: Sex: M/F

Family Status: Preg/Non-preg

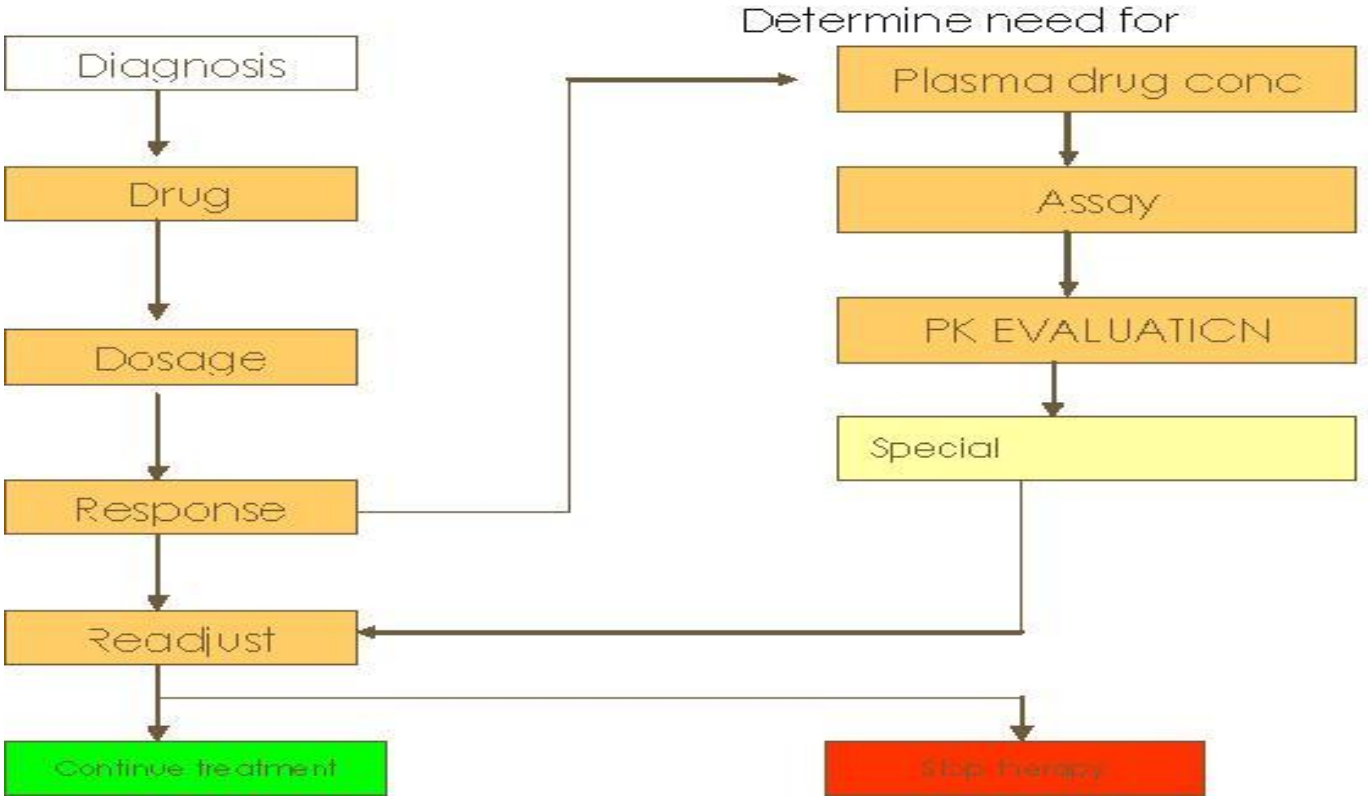
Time and last dose: Phone:

Time of blood sampling (drawing) AM/PM: _____

Drug administered: Digoxin

Drug	Dosage	Interval Route	Method of Assay	Expected Value	Actual Value	t½	Safety Range	Steady state	Remarks
Digoxin	Mg/kg	O/p b.i.d/ t.i.d	HPLC/ UV/ Immuno assay	-	-	Hrs	Mg/ml	-	-

Process of Therapeutic Drug Monitoring or Application of Pharmacokinetics in Clinical Situations:



CONCLUSIONS

- Therapeutic drug monitoring can be very effective tool to optimize drug therapy and minimize the risks of treatment specially for drugs that have narrow therapeutic window.
- Therapeutic drug monitoring can reduce the extent of hospitalization and contribute to better patient care.
- In every country there has to be an audit on the monitoring services to provide critical assessments of outcome and benefits.
- TCI on the other hand reflects an optimal concentration, balancing effectiveness and adverse effects.
- Therapeutic drug monitoring practice does not appear to have much clinical impact. It is more of a tentative approach.

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