Process of therapeutic drug monitoring:

The process of therapeutic drug monitoring in a given patient may be regarded as consisting of three important components. These three components are:

1. Development of plasma profile in each patient
2. Observation of clinical effects of drug in the patient
3. Interpretation and application of plasma concentration data in order to develop safe and effective dosage regimen.

1. Development of plasma profile:

The development of plasma profile of the drug in a patient involves withdrawal of blood samples at predetermined time intervals which involve the following steps:

a. Administering a predetermined dose of the drug:

- The amount of drug administered is usually based on manufacturer's recommendation, patient's condition, presence of other conditions/disease states and previous experience of the professional with the drug.
- All doses should be timed exactly for starting time and duration of administration.

b. Collection of blood samples:

- A single plasma drug concentration may not yield useful information unless other factors are considered which include: knowledge of dosage regimen of the drug, including size of the dose and dosage interval, route of drug administration, and time of sampling (peak, trough or steady state).
- In practice, through plasma concentrations

are easier to obtain than peak or average plasma concentrations during a multiple-dose regimen. Also there may be limitations to withdrawal of many blood samples.

- When the drug is administered extravascularly, blood sampling times for therapeutic drug monitoring should preferably during post-distributive phase for loading dose and at steady state for maintenance doses. This is because, after distribution equilibrium has been established, the plasma drug concentration during the post-distributive phase is better correlated with the tissue concentration and drug concentration at the site of action.
- When multiple blood samples are collected at various time intervals the time of collection of each blood sample is usually determined

• Ideally blood samples should be collected in direct venipuncture in clean glass tubes without anticoagulant, because of presence of heparin can result in increased free fatty acid concentrations, causing altered plasma protein binding.

C. Determination of drug concentration in each Sample:

• Analysis of blood for concentration of the drug is usually performed by either a clinical chemistry lab or a clinical pharmacokinetic lab.

• Any number of analytical techniques and methods may be used to determine concentration of drug in the plasma. Eg: Chromatography, fluorometry, spectrophotometry, immunoassay and radio isotopic methods.

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C. Determination of drug concentration in each Sample:

- Analysis of blood for concentration of the drug is usually performed by either a clinical chemistry lab or a clinical pharmacokinetic lab.
- Any number of analytical techniques and methods may be used to determine concentration of drug in the plasma. Eg: Chromatography, fluorometry, spectrophotometry, immunoassay and radio isotopic methods.

- The assay used should be specific for the drug molecule rather than the general structure of the drug.
- The assay should be able to distinguish the drug, its metabolites and endogenous and exogenous substance, because interference from other materials may be erroneously inflate the results.

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d. Plasma profile and pharmacokinetic model development:

- A plot of concentration of drug in the plasma as a function of time provides a wealth of information concerning the drug in an individual patient.
- The plasma profile could indicate whether the drug confers the characteristics of one,

two or three compartment model on the body.

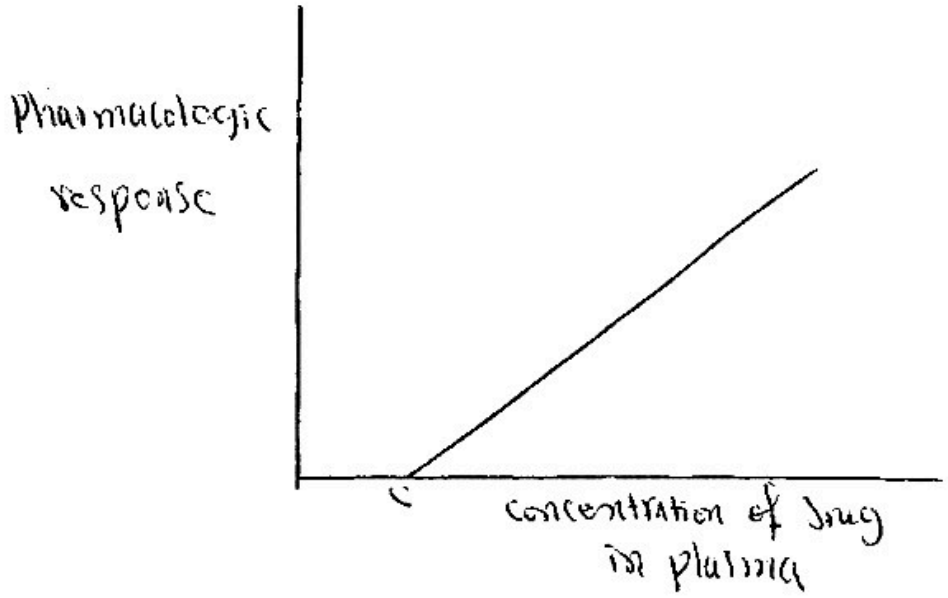
- The biological half life of drug can usually be estimated directly from the plasma profile and an indication of apparent volume of distribution can also be obtained from plasma profile.
- Plasma concentration data following intravenous injection of a rapid bolus dose provides partial characterization of drug disposition properties.
- Oral administration of drug provides additional pharmacokinetic parameters which are related to absorption and intrinsic clearance of the drug.

2. Clinical effects of drug:-

- The second component of the process of therapeutic drug monitoring relates to the relationship between the drug concentration at the site of action and the pharmacologic response

in the patient.

- Therapeutic drug monitoring using drug concentration data can be applied only when plasma concentration of drug exhibits a good correlation with the pharmacologic response.



- Following table lists a number of factors to consider when interpreting concentration of drug in the plasma:

- Pharmacokinetic evaluation of plasma concentration of drug:

- Plasma concentration correct but patient does not

respond to therapy

→ Drug interaction at receptor site

→ Altered receptor sensitivity (eg. Tolerance)

- Plasma concentration(s) higher than anticipated

→ Error in dosage regimen

→ Rapid bioavailability

→ Slow rate of drug elimination

→ Slower than anticipated apparent volume of distribution

→ Wrong drug product

→ Timing of blood sample

→ Incorrect assay methodology

→ Problem with patient compliance

- Plasma concentration (s) lower than the anticipated

- Problem with patient compliance

- Error in dosage regimen

→ Poor bioavailability

→ Rapid rate of drug elimination

→ Enlarged apparent volume of distribution

→ Steady state not reached

→ Timing of blood sample

→ Wrong drug product

→ Incorrect assay methodology

• Therapeutic decisions should not be based solely on plasma drug concentrations, but the clinician should evaluate the data using sound medical and pharmacologic judgment and observation.

3. Development of dosage regimen:

• The third component of therapeutic drug monitoring relates to development of dosage regimen based on concentration of drug in plasma.

- The concentration of drug in plasma can only be used as an indicator if the following assumptions are valid:

- The concentration of drug in plasma is the only indicator that can be used to develop dosage regimen.
- Upon administration, the drug confers the characteristics of one compartment pharmacokinetic model on the body.
- The intensity of pharmacologic response is proportional to concentration of drug in the plasma.

- Based on the above assumptions, a decision is made to formulate drug therapy regimen by clinical pharmacokinetic monitoring.

- The major steps involved in drug therapy

regimen are as follows:

a. Diagnosis:

Since diagnosis of patient's ailments more in the purview of physician treating the patient, it is assumed that a poor diagnosis has been made and drug therapy has been selected by the attending physician.

b. Drug product selection:

The selection of drug product for the treatment is usually the prerogative of the physician treating the patient. Sometimes clinical pharmacist is the part of selection process. The clinician may choose one drug over another based on a number of factors like presence or absence of pathophysiologic conditions, previous medical history of the patient, concurrent

drug therapy, and known allergies.

c. Dosage form selection:

The prescriber has the option of choosing administration of drug from a variety of commercially available dosage form. The choice of dosage form selected may affect clinical response, since bioavailability of a given drug often depends on the dosage form and the route of drug administration.

d. Dosage regimen:

A dosage schedule is now designed for the patient. This is generally based on the following considerations: recommendation of manufacturer concerning the size and frequency of administration of the drug dose, clinical experience of practitioner with the drug, and patient's medical history. (eg. Drug

sensitivity, known allergies, concurrent drug therapy, drug interactions, patient compliance, and presence of pathophysiologic conditions]. When designing the therapeutic dosage regimen, the following factors must be considered:

→ The physiology of the patient, i.e. age, weight, gender etc of the patient under treatment.

→ The pathophysiologic condition of the patient (eg. presence of renal impairment, hepatic disease, congestive heart failure which may alter the normal pharmacokinetic profile of drug.

→ Exposure of patient to other medication that may alter the usual pharmacokinetics of the drug.

→ Exposure of patient to environment factors (such as smoking) that may affect the usual pharmacokinetics of the drug.

→ The absorption, distribution and elimination profile of the drug.

→ The target concentration of drug at the receptor site for the patient under treatment, including any change in receptor sensitivity to drug.

→ The choice of drug dosage form.

e. Initiation of therapy:

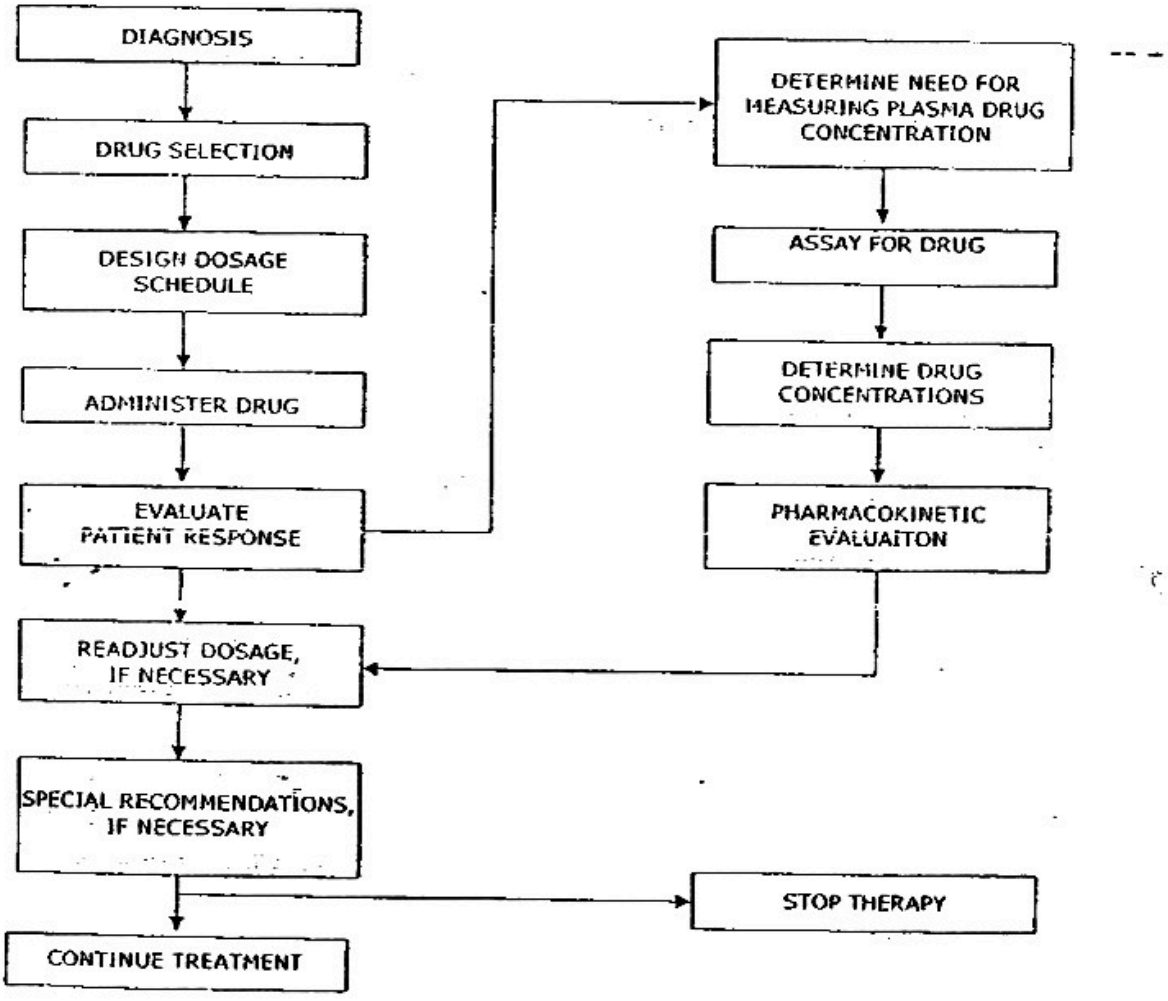
Therapy is initiated based on the dosage form and dosage regimen selected for the patient, and patient's clinical response to the treatment is monitored carefully.

f: Evaluation of clinical response:

- If the clinical response to treatment is satisfactory, an evaluation is made to determine whether the treatment should be continued

with the existing dosage regimen or the dosage regimen should be readjusted.

- If the clinical response is not satisfactory and/or unacceptable, then it may be necessary to revise the dosage regimen completely, and when this happens, a pharmacokinetic evaluation must be made.



g. Patient's compliance:

- Common problems associated with patient compliance may be due to neglect on the part of patient to follow instructions, or actual difficulty in compliance.
- There are many factors that may affect patient compliance which include: complicated instructions, multiple daily doses, forgetfulness on the part of the patient resulting either in skipping doses or taking more doses than prescribed, cost of medication, difficulty in swallowing the dosage form, and adverse drug reaction.
- In case of ambulatory patients, the patient must remember to take medication as prescribed in order to obtain optimal clinical effect of the drug. Therefore it is very important that the clinician must consider patients life-style and needs when developing dosage regimen.

h. Special recommendations:

. Sometimes it may be essential to give specific instructions to a patient in order to achieve the desired goal.

Eg: The patient may be taking the drug after a meal instead of before a meal, or the patient may not be adhering to a special diet (eg Fat free or low salt diet). In such cases the patient may not be responding to drug therapy as expected, and may need special simple and easy to follow instructions.