

CHAPTER - 7

THERAPEUTIC DRUG MONITORING – CONCEPTS, METHODOLOGY, CLINICAL APPLICATIONS AND LIMITATIONS

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INTRODUCTION

The aim of therapeutic research is to find out an effective medication against the disease without any dangerous toxic action. The delicate problem is that very often the dose of drug confuses with toxicity. Primary care physicians who understand the complexities of drug dosing may be able to provide their patients with more effective pharmacologic therapy. Standard or empirical methods of dosing are appropriate for most agents. The evolution of pharmacokinetics and the recent development of simple and reliable analytical technology has led to pharmacokinetic dosing, a more sophisticated and exact method of dosing certain agents. When used properly, measurements of plasma drug levels in the clinical setting may provide valuable information. While these drug levels often do allow more objective monitoring and titration of therapy the information also has the potential to be valueless or even misleading. This article will review the reasons why the dosage of most drugs should be individualized, the conditions that must be satisfied in order to make information about serum concentration helpful for dosage individualization and the many pitfalls and cautions encountered in the use of this information.

CONCEPT OF THERAPEUTIC DRUG MONITORING (TDM)

TDM is based on the principle that for some drugs there is a close relationship between the plasma level of the drug and its clinical effect. If such a relationship does not exist TDM is of little value. Like any diagnostic test, the measurement of plasma level is justified only when the information provided is of potential therapeutic benefit. The clinical value of plasma level monitoring depends on how precisely the treatment outcome can be

defined. When therapeutic outcome can be objectively and replicably quantified, such as during antithrombotic therapy with coumarin derivatives, little additional information is gained by plasma levels. On the other hand when a precise therapeutic end point is difficult to define, monitoring of drug levels may be of considerable therapeutic assistance.

TDM will be useful if the following criteria are met:

- 1) the drug in question has a narrow therapeutic range,
- 2) a direct relationship exists between the drug or drug metabolite levels in plasma and the pharmacological or toxic effects,
- 3) the therapeutic effect can not be readily assessed by the clinical observation,
- 4) large individual variability in steady state plasma concentration exists at any given dose and
- 5) appropriate analytic techniques are available to determine the drug and metabolite levels.

TDM is unnecessary when

- 1) Clinical outcome is unrelated either to dose or to plasma concentration
- 2) dosage need not be individualized
- 3) the pharmacological effects can be clinically quantified
- 4) when concentration effect relationship remains unestablished,
- 5) drugs with wide therapeutic range such as beta blockers and calcium channel blockers.

MAJOR INDICATIONS FOR TDM:

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While there may be specific individual circumstances for TDM, most indications can be summarized as follows:

1. Low therapeutic index
2. Poorly defined clinical end point
3. Non compliance
4. Therapeutic failure
5. Drugs with saturable metabolism
6. Wide variation in the metabolism of drugs
7. Major organ failure
8. Prevention of adverse drug effects

TCM OF ESTABLISHED VALUES:

1. Cardio active drugs : amiodarone, digoxin, digitoxin, disopyramide, lignocaine, procainamide, propranolol and quinidine
2. Antibiotics : gentamycin, amikacin and tobramycin
3. Antidepressants : lithium and tricyclic antidepressants
4. Antiepileptic drugs : Phenytoin, phenobarbitone, benzodiazepines, carbamazepine, Valproic acid and ethosuximide
5. Bronchodilators : theophylline
6. Cancer chemotherapy : methotrexate
7. Immunosuppressives : cyclosporine

ANALYTICAL METHODOLOGY:

The methods currently available for analyzing data obtained in drug disposition studies are enormous. The fundamental procedures necessary for the quantification of the drug in the body are: recovery from body fluids, tissues, and organs, separation from the biological components, identification of the species concerned and finally quantification. The analytical methodology employed should ideally: 1) distinguish between compounds of similar structure – unchanged drug and metabolites. 2) detect small amounts 3) be simple enough to use as a routine assay and 4) be unaffected by other drugs administered simultaneously.

Spectrophotometry and Fluorimetry: Prior to advent of GLC and HPLC, drug samples were analyzed by spectrophotometric methods. Solvent extraction schemes coupled with a spectrophotometric finish can still provide a much derived simplicity in assay procedure when the level of sensitivity required is not too low. i.e. in the ug/ml range. However the drawbacks are large volume of samples, complex extraction procedures and interference by other compounds.

Thin layer chromatography (TLC): TLC possess adequate resolutions for identifying many drugs but it suffers from inability to quantify these drugs accurately and time consuming technique with inadequate sensitivity. However it is a useful techniques in toxicology laboratory.

HPLC and GLS: These methods are highly specific, precise and sensitive. Besides multiple analyses can be done. The drawbacks are i) extraction step required ii) slow, single serial analysis, iii) column degenerates with time and iv) complex analyses require considerable processing. Out of these two, HPLC technique is superior because thermolabile compounds can also be analyzed.

Radio immuno assay (RIA): It is sensitive, reasonably precise but requires the use of radionucleides. Cross reactivity with other closely reacted drugs is a potential problem with this technique. Besides it is not possible to find out the optically active isomer. The hazards of using

radioactive material is a considerable limitation of this method.

Enzyme Immuno assay: These techniques offer some advantages over RIA in that no radioactive tracer is required; there is no need to separate the bound from the unbound fractions. However the potential for cross reactivity still exists. Burgess et al³ compared serum phenytoin concentration in patients with normal renal functions and in patients with end stage renal disease using EMIT and GLC and found that in patients with renal insufficiency and EMIT values were 90% higher than GLC values, Digoxin RIA remains as one of the most precise and sensitive methods for quantitation of digoxin in patients serum⁴.

Fluorescence polarization Immunoassay (FPIA): This assay procedure combines competitive protein binding with fluorescence polarization to give direct measurement without the need for a separation procedure. The advantages of this method are accuracy, precision and short turn around time. Apple et al⁵ compared three methods viz., FPIA, EMIT and HPLC for measurement of total and free phenytoin levels in uremic patients and found interferences in EMIT assays were minimal and that FPIA and HPLC determinations are in agreement.

INTERPRETATION OF SERUM DRUG CONCENTRATION AND ADJUSTMENT OF DOSAGE:

Drug concentration determinations must always be interpreted in the context of the clinical data. Therapeutic ranges are available but should be used only as a guide. Many factors alter the effect of a drug concentration at the site of action, e.g., serum concentration of digoxin that is therapeutic for most patients may be excessive for a patient with hypokalemia. Furthermore range of serum drug concentration require adjustment when other drugs with synergistic or antagonistic actions are administered concomitantly.

MAJOR CAUSES OF UNEXPECTED SERUM CONCENTRATION IN PATIENTS:

The most important causes of unexpected serum concentrations are non compliance,

inappropriate dosage, malabsorption, poor bioavailability, drug interactions, hepatic or renal disease altered protein binding and genetic factors. If these factors can not be eliminated, a dosage adjustment is required. For drugs with linear kinetics the following formulae may be used:

$$\text{New dose} = \text{Old dose} \times \frac{\text{Desired drug concentration}}{\text{Old drug concentration}}$$

Timing of Sample collection:

The importance of proper timing of a sample is not given sufficient attention while ordering measurement of a plasma concentration¹. The best sampling time is in the predose or through phase just prior to a maintenance dose, when a drug is administered by multiple oral doses. This principle is important for digitalis which is administered on a once daily basis in the morning. For drugs with a long half life such a phenytoin atleast 4 to 5 half lives must elapse before a sample is taken. A knowledge of usual half life ranges will thus be useful.

Sample timing for some important drugs:

a) Phenytoin: Since phenytoin has a long half life a single daily dose may be employed and so the timing of concentration monitoring is not critical⁶.

b) Carbamazepine: Its half life may be as long as 48 h following a single dose. A trough concentration taken just after a dose together with a peak level three hours later is ideal.

c) Digoxin: The measurement must be made atleast six hours after a dose to avoid inappropriate high levels.

d) Theophylline: This drug has a narrow therapeutic index and timing of sampling is not critical if the patient is receiving one of the slow release formulations.

e) Lithium: A 12 hr sample gives the most precise guide to dosage adjustment.

- f) Phenobarbitone: Any time sample is sufficient
- g) Gentamicin: Pre dose peak; 0.5 hr after i.v. and 1 hr after i.m. administration.

DOSAGE REGIMEN:

It is one of the factors to be considered while interpreting TDM data. It is important to know the duration of drug therapy, dosage and when the last dosage was taken.

ACTIVE METABOLITE:

Many drugs are biotransformed into compounds that are pharmacologically active. When evaluating the therapeutic effect of such drugs, the relative contributions of all active substances present in the serum must be integrated e.g. imipramine is biotransformed to the active metabolite – desipramine.

EFFECT OF DISEASE STATES:

Acute or chronic disease alters drug clearance patterns. Thus drug concentrations may be elevated or depressed depending on the pathophysiology of the system involved, e.g., liver disease impairs the clearance of drugs dependent upon conversion to more water soluble compounds. Congestive cardiac failure can precipitate elevated drug levels of agents dependent on hepatic metabolism for clearance.

FREE DRUG MONITORING:

Development of new filtration devices (equilibrium dialysis, ultrafiltration, ultracentrifugation) has made it possible to measure free unbound drug levels in serum⁷. The advantages are that the free concentrations is independent of changes in plasma binding and is the pharmacologically active concentration. The disadvantages are that it is time consuming, expensive and therapeutic ranges do not yet exist for many drugs.

USE OF SALIVA IN DRUG MONITORING:

The concentration of a drug in saliva is proportional to the concentration of the unbound

rather than to the total of bound and unbound drugs in plasma⁸. The practice of measuring drugs in saliva is appealing because it is non invasive. However it has its limitations viz., some substances such as lithium are actively secreted into the saliva rather than by passive process. Drug binding to salivary proteins may produce discrepancies in plasma/salivary ratios, e.g. phenytoin⁹. Drugs may also bind to oral cell debris, e.g. propranolol, Salivary flow may be reduced in patients taking anti cholinergic drugs. Preparations used to stimulate salivary flow might interfere with drug estimation e.g. lemon flavored sweets interfere with amitriptyline estimations.

EFFECT OF AGE:

Variability in response to drugs occurs at extremes of age. Elderly patients are more sensitive to the CNS depressant effect of drugs but are less sensitive to cardiovascular effects of propranolol. On the other hand young children are more sensitive to CNS depression effects of morphine. However more data are needed on the effects of age on pharmacokinetic and pharmacodynamics of drugs to allow optional individualization of dosage.

PREGNANCY:

Little has been published on the monitoring of plasma drug levels during pregnancy. Plasma drug levels of phenytoin and phenobarbitone tend to reduce during pregnancy.

COST EFFECTIVENESS:

The measurement of drug levels in body fluids must be cost effective. The cost of performing an individual test is determined by the summing equipment, personnel, supply and overhead expenditure for a given period of time and dividing that amount by the number of assays performed in the same time interval. The fee charges is then determined by the test's cost plus desired profit. The foregoing calculations produce an unreasonably expensive fee although high fee for unique tests requiring special methods may not be unreasonable. Cost-benefit analysis of gentamicin dosage regimens of burn patients with gram

negative septicaemia showed that a cost benefit ratio of 8.7 to 1 10 with decreased mortality and increased economic productivity. Mungall et al¹¹ showed that use of clinical pharmacokinetics by therapeutic drug monitoring service offered substantial benefits like fewer adverse reactions, shorter intensive care unit stay and shorter overall hospital stay.

CLINICAL USEFULNESS OF TDM:

TDM data provides the clinician with greater insight into the factors determining the patients response to drug therapy. For example when a patient fails to respond to a usual therapeutic dose, measurement of plasma level can help to distinguish a noncompliant patient and a patient who is a true non-responder. TDM also provides useful information regarding individual variations in drug utilization patterns and alteration in drug utilization as a consequence of altered physiological state or disease process.

TDM is a useful adjunct in treating many patients provided the potential pit falls and problems are considered.

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