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APPRAISAL OF THERAPEUTIC DRUG MONITORING

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ABSTRACT:

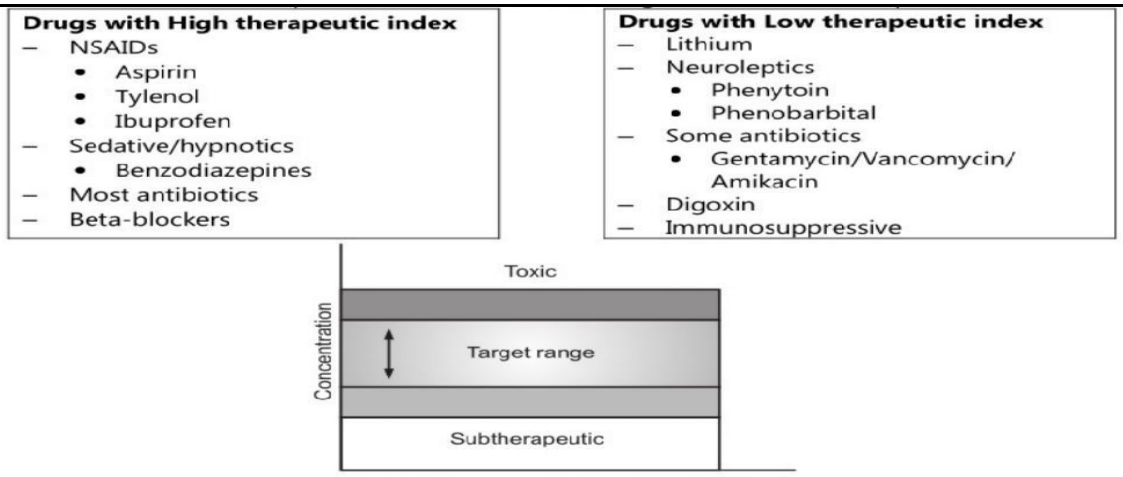
Therapeutic drug monitoring could be a branch of clinical chemistry and clinical pharmacology that specifies within the measurement of medication levels in blood. Its main fixate is on drugs with a narrow therapeutic range.TDM begins when the drug is first prescribed, and involves determining an initial dosage process relevant for the clinical condition and such patient characteristics as age, weight, and collateral drug therapy. When interpreting concentration measurements, factors that require to be considered include the sampling time in reference to drug dose, dosage history, patient response, and therefore the desired medicinal targets. The goal of TDM is to use suitable concentrations of medications to optimize clinical outcomes in patients in various clinical situations.

Index Terms-

Therapeutic, pharmacology, monitoring, fixate, clinical, medications, interpreting,optimize.

INTRODUCTION:

Therapeutic Drug Monitoring (TDM) is defined because the utilisation of drug measurements in body fluids as an aid to management of patients receiving drug therapy for the cure, alleviation or prevention of disease[1].The main goal is that the optimization of the dosage regimen which might provide adequate and safe drug therapy through maintaining blood drug concentrations within a therapeutic range or window[2].Therapeutic drug monitoring (TDM) has been accustomed individualize drug therapy since the primary 1970s[3]. Therapeutic drug monitoring is beneficial for patient management where it's established that good correlation exists between pharmacological response and serum drug concentration [4].The aim of TDM is to optimize pharmacotherapy by maximizing therapeutic efficacy, while minimizing adverse events, in those instances where the blood concentration of the drug could be a better predictor of the specified effect(s) than the dose [3].Each individual varies in biological process thus supported metabolism the medication doses are differ in each patient [5].



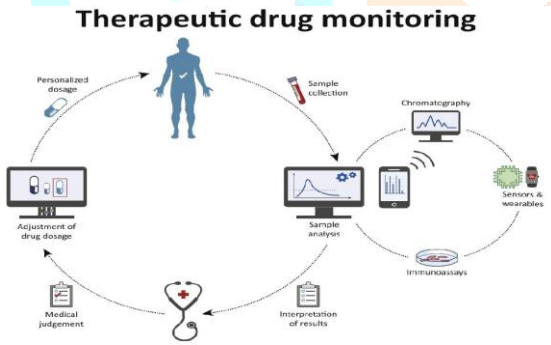
(Fig.1)Therapeutic Drug Monitoring[5]

OVERVIEW OF THERAPEUTIC DRUG MONITORING:

TDM should include the active management of free drug concentrations in physical body fluids using either chromatographic or immunoassay-based methods or on-site solutions (sensors and wearables) for the optimum good thing about each individual patient [6].

(Fig.2) Therapeutic Drug Monitoring

[6]



WHICH DRUGS?:

The most commonly monitored drugs are carbamazepine, valproate and digoxin [7].

Table :1

Drugs suitable for therapeutic drug monitoring

Drug	Target range *
Drugs regularly monitored in clinical practice	
digoxin	0.8–2 microgram/L and < 0.01 microgram/L in refractory heart failure
lithium – acute mania	0.8–1.2 mmol/L
– maintenance	0.4–1.0 mmol/L
perhexiline	0.15–0.6 mg/L
phenytoin	10–20 mg/L
cyclosporin	50–125 microgram/L (serum or plasma) 150–400 microgram/L (whole blood) Concentrations differ for various clinical settings
sirolimus	5–15 microgram/L (whole blood)
tacrolimus	5–20 microgram/L (whole blood)
Drugs for which monitoring may be useful	
amiodarone	1–2.5 mg/L
carbamazepine	5–12 mg/L
flecainide	0.2–0.9 mg/L
lamotrigine	1.5–3 mg/L
salicylate	150–300 mg/L
sodium valproate	50–100 mg/L
vancomycin	Trough 10–20 mg/L

* Concentrations may vary between laboratories

[7]

- **Amikacin injection**: 250 mg (as sulfate)/mL in 2- mL vial
  FIRST CHOICE
  -pyelonephritis or prostatitis (severe)
  SECOND CHOICE
  - high-risk febrile neutropenia
  - sepsis in neonates and children [c]
- **Gentamicin** : 10 mg; 40 mg (as sulfate)/ mL in 2- mL vial.
  FIRST CHOICE
  - community acquired pneumonia (severe) [c]
  - complicated severe acute malnutrition [c]
  - sepsis in neonates and children [c]
  SECOND CHOICE
  - Neisseria gonorrhoeae
- **Vancomycin capsule**: 125 mg; 250 mg (as hydrochloride).
  SECOND CHOICE
  - C. difficile infection
  Powder for injection: 250 mg
  SECOND CHOICE
  -high-risk febrile neutropenia[16]

Therapeutic drug monitoring (TDM) is especially useful within the following situations:

1. Drugs with low margin of safety,
   e.g.-digoxin, anticonvulsants,
   antiarrhythmics, lithium, tricyclic
   antidepressants.
2. If individual variations are large
   e.g.- antidepressants, lithium.
3. Potentially toxic drugs utilized in the presence of nephrosis
   e.g.- aminoglycoside antibiotics,
   vancomycin.
4. In case of poisoning.
   In case of failure of response with
   none apparent reason,
   e.g.- antimicrobials
5. To check patient compliance,
   e.g.- psychopharmacological

agents.[8]

CLINICAL IMPLICATIONS FOR A DRUG WITH NARROW THERAPEUTIC RANGE:

Drugs with narrow therapeutic index(i.e.drugs with little difference between toxic and therapeutic doses) such as warfarin,lithium,digoxin require therapeutic drug monitoring(TDM) both to achieve therapeutic levels and to minimize toxicity.Drugs with broad therapeutic index such as amoxicillin are safer as very high doses are required to result in toxicity.

Therapeutic index = toxic dose/
effective dose[9]

FACTORS AFFECTING THE THERAPEUTIC DRUG MONITORING (TDM):

1. **Pharmacokinetic variability** : There is lack of patient compliance leads to insufficient plasma drug concentration to achieve optimum therapeutic effect.
2. There is influence of certain ages such as: neonates, children and elderly on various pharmacokinetic parameters which results into the alterations in the therapeutic response as well as plasma drug concentration.
3. There is also influence of various pathological/disease conditions such as, hepatic, renal and respiratory on the pharmacokinetic properties of drug.Thus,it may cause difficulty in estimation of TDM.[5]
4. **Active metabolites**: The clinician may additionally use TDM to observe drug levels to spot the clinical output of active metabolites. Therapeutic drugs present special problems when these drugs are metabolized to compounds that are active pharmacologic and a few metabolites that have an identical structure to the parent drug. During monitoring of serum drug level that metabolites show false-negative results and should apparently increase obtained plasma levels.[2]
5. **Testing methodology**: there must use a correct analytical method for estimation of TDM.It is important to contemplate the sensitivity and specificity of the test method.For example-TDM isn't suitable for anticoagulant effect which may be effectively estimated by using functional laboratory test.
6. **Blood sampling timing**: Appropriate timing of a blood sample plays a crucial role while ordering TDM. Proper timing is a vital tool in TDM. All drugs which are considered under TDM service must be taken at their recommended timing.Some TDM drug timing is mentioned below :
    1. Carbamazepine: The Half-life can be longer than 48 hours ensuring one dose. Recommended a trough concentration just after the dose followed by a peak level 3 hours later.
    2. Digoxin: Guidance for sample six hours after a dose is usually recommended to flee inappropriate concentrations.
    3. Gentamicin: Pre-dose and peak (0.5 hours after I.V. and 1 hour after intramuscular administration).
    4. Lithium: 12 hours sample gives the foremost appropriate guide to dose Adjustments.
    5. Phenobarbitone: Any time sample is taken, timing isn't crucial.
    6. Phenytoin: it's an extended half-life that the timing of concentration monitoring isn't critical.
    7. Theophylline: contains a narrow therapeutic range and timing of the sampling isn't Critical if the patient is receiving one amongst the slow-release preparations.[2]

Protein binding: There is alteration in the protein binding capacity of drugs in various pathological conditions and during drug interactions which resulted into change in the concentration of bound and unbound drug this leads into loss of efficacy or drug toxicity.Thus, there is a need to consider effect of protein binding while interpreting results of TDM.[5]

- **Effect of pregnancy:** Newer antimicrobials are excluding pregnant women for reasons of risk avoidance and, therefore,prescribers must depend on post-marketing surveillance data.[2]The clinician must consider the advantages of drug treatment for the pregnant mother versus the danger to the fetus,before prescribing medications during pregnancy. [10] For example-An important a part of the care of pregnant women with epilepsy includes vitamin B complex supplementation and regular monitoring of their AEDs before, during and after the pregnancy, including measurement of AED concentrations in mammary milk when breast-feeding is going on.[11]

METHODS FOLLOWED FOR TDM:

There are various methods followed for TDM services. The gold standard used for many drugs is High Performance Liquid Chromatography (HPLC) but it's cumbersome and requires skilled manpower to keep up operation.The introduction of immunoassays have helped greatly within the easy availability of drug levels.Radioimmunoassays,Enzyme Immunoassays (EIA), Enzyme - Multiplied
ImmunoassayTechnique(EMIT),
Fluorescence Polarization Immunoassays (FPIA) and Chemiluminescence have proved to be the cornerstones for the widespread adoption of immunoassays for drugs in clinical laboratories.[1]
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Apart from the limited number of medication amenable to therapeutic drug monitoring, there are inherent limitations, including the scientific accuracy of the drug assays, laboratory variability in reporting, limited accessibility in rural Australia and then the validity of suggested target ranges.[7]Monitoring of therapeutic drugs is costly in terms of equipments, supplies, technical experts to induce concentration in biological fluid, to interpret and investment in research data collection etc.[12]The range describes a spread of drug concentrations associated with a reasonable probability of efficacy without undue toxicity within the bulk of patients. It is not well described for several drugs and is sometimes supported by a awfully limited number of data point.[7] Only those drugs with broad therapeutic range are benefited by the monitoring. The info on the population of males of CHF younger than 50 years with normal value of renal cardiac function is accessible. However, the values are different for female patients older than 70 years suffering from CHF that can't be interpreted from the available data on normal values.For certain drugs,
values of serum concentration are less justifiable than the values of pressure level measurements and blood clotting. the information on serum concentration isn't
required for the drugs with broad therapeutic range.[12]

INTERPRETATION:

Even if an appropriate specimen is taken
and an accurate analysis is obtained, the full exercise is valueless unless the results correctly interpreted and any necessary action taken.[1]Drug concentrations have to be interpreted within the context of the individual patient without rigid adherence to a firing range. for instance, if a patient has an medicinal drug concentration just under the practice range, but isn't having seizures, a rise in dose probability isn't required.[7]Expert clinical interpretation of
the concentration measurements are invaluable inorder to derive any meaningful clinical enjoyment of the procedure. It's important to notice that therapeutic ranges are mere recommendations supporting the clinical response of atiny low group of patients taking the drug. [4]Before making dose adjustments, it's important to think about if the sample was taken at the right time with relation to the last dose, if a gentle state has been reached and whether the patient has adhered to their treatment.[7]The therapeutic range may be a synthesis of two concepts - the minimum effective concert ration for a drug and also the maximum safe concentration. There is
evidence that drugs may be effective in some patients at supposedly subtherapeutic' concentrations.[1]

FUTURE:

Therapeutic drug monitoring or TDM is
apparently very useful comprehensive studies recommended that it could be more beneficial if we used it with the help of proper guideline.[2]Developing countries differ from developed ones in having weak health-care structures, inadequate financial resources, unreliable supply and quality of pharmaceuticals lack of adequate drug legislation and policy and a high rate of inappropriate self medication.priorities for health care services are radically different from those in developing nations.[13] As patient exhibit widely varying pharmacokinetic and pharmacodynamic
Responses, they need careful management.
Increasingly, pharmacogenomics is being used to identify genetic variants which might impact on drug behavior both in terms of its blood distribution/concentration and consequent efficacy and in terms of its toxicity.[11]Point of care (POC) assays are analytical devices that provide clinically relevant information without the need for a core clinical laboratory.The pharmaceutical industry is increasingly using population modelling techniques in a model-informed drug design and development (MID3) framework.[14]One of the important approaches which really work is to arrange awareness program like conferences, lectures and newsletters, multidisciplinary quality improvement efforts, proper TDM services, can be enhanced by developing computer-based software.The clinician can improve TDM service by arranging education programs to provide knowledge to the pharmacist,nurses;clinical
Pharmacists and with the help above all
Approaches to provide better results of TDM.World health organization must allocate charity funds for procurement costly equipment to promote TDM service in poor countries.[2]

CONCLUSION:

Therapeutic drug monitoring (TDM) is important tool in health care sector.The use of TDM requires a combined approach encompassing pharmaceutical, pharmacokinetic, and pharmacodynamic techniques and analyses.The drug concentration is complementary to and not a substitute for clinical judgement so its important to treat the individual patient and not the laboratory value.Regular monitoring of drug is required.Coordination of Clinical team which incorporates clinician, paramedical staff and clinical pharmacist can enhance this practice.Rather, TDM plays an important role within the development of safe and effective therapeutic medications and individualization of those medications. Additionally, TDM can help to spot problems with medication compliance among noncompliant patient cases.The principle and practice of therapeutic drug monitoring should be emphasised within the continuing medical education lecture series periodically organized to update health practitioners.TDM could be a fundamental tool it should be used effectively.

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