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Evaluation of the knowledge of Health Care Professionals regarding Therapeutic Drug Monitoring in Public Hospitals of Lahore, Pakistan

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Abstract *A cross sectional study was performed among 250 health care professionals from Children Hospital, Jinnah hospital and Services Institute of Medical science Lahore, through a self-designed questionnaire to assess the knowledge of therapeutic drug monitoring (TDM). A total 300 questionnaires were distributed and 250 were returned, giving a response 83%. Out of 300 health care professionals 50 participants don't even know the term TDM. Only 40% participants strongly agreed that TDM is done for all patients. Only 26.8% participants agreed that TDM is carried out for all drugs. Only 63.2% participants agreed that the TDM is very costly process. Only 38.4% strongly agreed that TDM requires extra time of health care professionals and only 36% participants remain neutral to the perception that TDM is requested by patient rather than health care professionals. Limited resources and lack of technical skills are barriers in performing TDM in under-developed country like Pakistan*

Key Words: Therapeutic Drug Monitoring, Drug Concentration, Health Care System, Therapeutic Index

Introduction

Therapeutic drug monitoring is the process of measuring the drug concentrations in plasma, serum or blood. This information is utilized to design individual dosage so that drug concentrations can be maintained within a desirable range. Drug concentration at the site of action is not checked routinely, on the other hand, the desired or adverse effects may correlate better with plasma or blood concentrations rather than they do with dose. Appropriate drug concentration levels are achieved by a team work which is usually comprised of nurses, doctors and pharmacists. A thorough collaboration is required among team members to maximize the results of therapeutic drug monitoring. Measuring plasma drug concentration is helpful mostly but still it cannot be done in several cases. Poor Plasma drug concentration shows poor compliance of drug or it predicts under treatment. Poor compliance may be due to following reasons i.e., if the patient is prescribed a dose which is unlikely be the reason of low concentration or if a previous measurement predicted that the plasma concentration ought to be higher for the given dose. The clinicians generally use indicators like blood pressure, blood glucose, clotting factors to predict the plasma concentration. However, for the drugs for narrow therapeutic ranges, therapeutic drug monitoring is advisable. The physician should measure the concentration of drug in plasma before strategizing the therapy. This would help him formatting the individual dose for individual patients. This method to individualize dosing is applicable for drugs with narrow therapeutic range as

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well as antibiotics. Concentration monitoring of all the drugs is not recommended nor is it achievable due to restricted resources. The monitoring of serum concentration can be fruitful for the measurement of concentration of drugs when there is poor correlation between drug dose and its clinical outcome. In such situations measuring the dose could be helpful to suggest the pharmacological effects of drug. Basically, TDM studies are of immense importance for drug with minimum correlation between dose and clinical result of dose (wide inter individual pharmacokinetic variation). The therapeutic index (therapeutic ratio, toxic-therapeutic ratio) for a drug shows the boundary between the therapeutic dose and the toxic dose. For most patients (exception is for hypertensive patient) penicillin contains a high therapeutic ratio therefore it could be given in higher doses with no compulsion to check for concentration acquired. On the other hand, the drugs with low therapeutic index like aminoglycosides, cyclosporine, anticoagulant, a constant monitoring is advised to keep the concentration in check and toxicity levels at bay. The ideal drugs to perform therapeutic drugs are antibiotics, analgesics, antiepileptic, and antiarrhythmic.

Common Characteristics for TDM

- Drug with an established relationship between its SDC (serum/blood drug concentration) and therapeutic response and/or toxicity.
- Drug with a narrow therapeutic index, Example: Lithium, phenytoin, and digoxin.
- Drug with large individual variability at steady state SDC in any given dose.
- Drug with poor relationship between its SDC and dosage.
- Drug with a saturable metabolism Example: phenytoin
- Drug with poorly defined end point or difficult to clinically predict the response. Example: immunosuppressant drugs.
- Drug whose toxicity is difficult to distinguish from a patient's underlying disease. Example: Theophylline in patients with chronic obstructive pulmonary disease.
- Drug whose efficacy is difficult to establish clinically. Example: Phenytoin

Methods for Performing Therapeutic Drug Monitoring

Therapeutic drug monitoring requires the collaboration of various disciplines such as pharmacokinetics, pharmacodynamics, and laboratory analysis. The idea of determining the pharmacokinetic parameters on analytical parameters is not recommended. The purpose of having Analytical goals in therapeutic drug monitoring must be focused on knowing the issue to be tackled, strategy to be used, and method to solve the given problem. If plasma drug concentration measurements are of any importance, then attention should be given to timing of blood sampling, the type of blood sample and to the technique which is to be used for the evaluation of results. Above all, it is pivotal to gather the blood sample for measuring the drug concentration at the right time after dosing. Mistakes in the timing of sampling would be responsible for the highest number of errors in the evaluation of the results. Mostly, the blood sample is collected into heparinized tube and maybe allowed to get clotted and no restrictions are put on the storage before measurement of required parameter. However, there are various protocols for drugs with narrow therapeutic range, e.g., for lithium and aminoglycosides, the blood samples must let to clot, and must be separated within the time span of one hour. For immunosuppressant like cyclosporine, consultation with the local laboratory is important to device the proper method on techniques of sampling and the timing after dosing. The techniques which are usually employed at the local laboratories and hospital are HPLC, fluorescence polarization immunoassay (FPIA), enzyme immunoassay (EMIT), and enzyme-linked immunosorbent assay. These assays are however sensitive to many antibodies present in drug compounds therefore it may sometimes result in falsely detected compounds. Pakistan is a developing country. A relentless struggle goes in to provide medicine to the majority of the population at agreeable and economical cost and bioavailability studies are performed only at the time of getting marketing approval. In Pakistan, quality of drugs does not meet standards therefore there is a need to have an additional quality control management. The TDM service may prove an important early indication of poor standard drugs.

Study Design and Methodology

After thoroughly studying many drugs and their possible side and adverse effects it was decided to perform a survey on assessing the knowledge of health care professionals regarding drugs and the potential outcomes of
their concentration. Therefore, A cross sectional study was designed to assess the knowledge of therapeutic

drug monitoring and its various aspects among health care professionals through self-design questionnaire.

Self-Design Questionnaire

The questionnaire includes information related to simple terms like therapeutic drug monitoring, its various terms like MTC, MIC, Therapeutic window, narrow therapeutic ranges, techniques employed to access the therapeutic drug monitoring. The questionnaires were distributed among 300 hundred health care professionals include nurses, doctors and pharmacists from three public hospitals of Lahore Pakistan, Children hospital, Services institute of Medical Science and Jinnah hospital. 250 questionnaires were returned.

Sample Technique

Was Non probability technique of sampling (using convenient sampling).

Duration of Study

Was from May 2019 to October 2019.

Hospitals and Targeted Audience

Three public hospitals: Children hospital, Services Institute of Medical Sciences, Jinnah Hospital Lahore, were selected and their health care professionals (nurses, doctors, pharmacists and laboratory technicians) for the study.

SPSS and Applied Statistics

Date was assembled through SPSS and applied statistics through on it to conclude this research project.

Results

A total of 300 questionnaires were distributed and 250 returned, giving a response rate of 83.3%. The very high response may be due to face-to-face interaction with the study participants. Non-respondents were not followed up. The demographic profile of health care professionals including gender and their job are shown in Table no.1.

Table 1. Demographic Profile of Study Participants

Variables	N(%)
Gender	
Male	112 (44.8%)
Female	138 (55.2%)
Job in hospital	
Nurse	49 (19.6%)
Medical officer	50 (20%)
House officer	68 (27.2%)
Specialist	31 (12.4%)
Hospital pharmacist	52 (20.8%)

Descriptive statistics for each item in the questionnaire is given in Table no.1 to Table no.3. Table no. 1 is related to demographic profile of study participants which are health care professionals. In our study females participated more as compared to males. The health care professionals especially nurses, medical officers, house officer, specialists and hospital pharmacist respond to our TDM questionnaire. The response of participants towards the therapeutic drug monitoring (TDM) were accessed by the questions focusing on the knowledge-based questions including the definition of TDM, MTC, MEC, Therapeutic window, trough concentration, peak concentration, purpose of TDM and the most recommended methods for measuring TDM. Out of 300 health care professionals 50 participants don't even know the term TDM.

Table 2. Responses to TDM knowledge Items

TDM knowledge-based items	N (%)
1. TDM is	
Measurement of drug conc. in blood	152(60.8%)
Measurement of level of drug toxicity in blood	25(10%)

TDM knowledge-based items	N (%)
Measurement of patient drug abuse	23(9.2%)
Measurement of required drug dose	50(20%)
2. TDM is indicated when	
The prescribed drug has narrow TI	74(29.6%)
The consequences of overdosing and under dosing are serious	40(16%)
Patients with chronic kidney diseases	20(8%)
Both a and b	116(46.4%)
3. MTC is	
Min conc. required for therapeutic effect	120(48%)
Min conc. in which toxicity usually occur	64(25.6%)
Conc. of drug that produce therapeutic effect	30(12%)
Unknown conc. of drug	36(14.4%)
4. MEC is	
Min conc. of drug required for therapeutic effect	129(51.6%)
Max dose of drug for therapeutic effect	21(8.4%)
Max effective dose	79(31.6%)
Drug of unknown conc.	21(8.4%)
5. Therapeutic window is	
Ratio b/w 2 effective doses	29(11.6%)
Ratio b/w MEC and MTC	139(55.6%)
Both	62(24.8%)
None	20(8%)
6. Trough conc.	103(41.2%)
Lowest conc. of drug in blood stream before next dose	92(36.8%)
Highest conc. of drug in blood before reaching therapeutic window	
None of these	33(13.2%)
Not specified	22(8.8%)
7. Peak conc. Is	
Lowest conc.	6(2.4%)
Highest conc. in blood stream	187(74.8%)
Highest and lowest conc.	41(16.4%)
None of these	16(6.4%)
8. Purpose of TDM	
To ensure medication dose is at therapeutic range	49(19.6%)
To avoid or anticipate toxic conc.	76(30.4%)
To monitor unexpected lack of efficacy	13(5.2%)
All of these	112(44.8%)
9. Most common recommended method for TDM	
HPLC	85(34%)
GC	77(30.8%)
Immunoassay	88(35.2%)

Attitude towards TDM was accessed by asking 5 questions as shown in Table no.3. Only 40% participants strongly agreed that TDM is done for all patients. Only 26.8% participants agreed that TDM is carried out for all drugs. Only 63.2% participants agreed that the TDM is very costly process. Only 38.4% strongly agreed that TDM requires extra time of health care professionals and only 36% participants remain neutral to the perception that TDM is requested by patient rather than health care professionals.

Table 3. Attitude towards TDM

Domain	Question No.	Strongly agree	Agree	Neutral	Strongly disagree	Disagree
Attitude	1	100(40%)	38(15.2%)	55(22%)	15(6%)	42(16.8%)
	2	63(25.2%)	67(26.8%)	45(18%)	26(10.4%)	49(19.6%)
	3	79(31.6%)	79(31.6%)	72(28.8%)	11(4.4%)	9(3.6%)
	4	96(38.4%)	84(33.6%)	38(15.2%)	22(8.8%)	10(4%)
	5	23(9.2%)	48(19.2%)	90(36%)	39(15.6%)	50(20%)

Discussion

Therapeutic drug monitoring also helps in assessing the possible outcomes of drug-drug interactions so while assessing the therapeutic drug monitoring various other associated factors came to surface. According to the report of WHO, there is a lack in proper setting of system of surveillance of drug -drug interactions, multi drug prescribing, poly pharmacy. These issues indicate many underlying systematic loops. Doctors are overburden and disproportionality between population and facilities add up to these problems. In the similar report, it is reported that the quantity of drugs prescribed in Pakistan is higher than any other health care of world. Moreover, the missing setup of clinical pharmacology and undefined roles of pharmacist are also putting pressure on physicians. After drug prescription, the outdoor patients take up drugs without any possible monitoring. There are fewer studies which explore the situations related to drugs and its therapeutic drug monitoring in Pakistan. Anyhow, in Pakistan , with the limited and restricted resources and population pressure on hospitals, Therapeutic drug monitoring came into being in hospitals around 1980s and it has grown remarkably since then with the setting of new departments like clinical pharmacology . Therapeutic drug monitoring is performed in both public sector large hospitals with teaching facilities and also in well-established private hospitals. In public health sector, TDM is done through the setup of clinical pharmacology and in private hospitals it is performed through biochemistry departments with least interpretations. A cross sectional study regarding awareness of TDM in health care professionals and how much there is practice of TDM in Pakistan was conducted. A self -designed questionnaire was designed and was filled by doctors, pharmacists and nurses from Jinnah hospital, services institute of medical science and Children hospital. The results show that there is lack of practicing TDM in Pakistan as compared to other countries. A total of 300 questionnaires were distributed and 250 returned, giving a response rate of 83.3%. The very high response may be due to face-to-face interaction with the study participants. Non-respondents were not followed up. The response of participants towards the therapeutic drug monitoring (TDM) were accessed by the questions focusing on the knowledge-based questions including the definition of TDM, MTC, MEC, Therapeutic window, trough concentration, peak concentration, purpose of TDM and the most recommended methods for measuring TDM. Out of 300 health care professionals 50 participants don't even know the term TDM. Only 40% participants strongly agreed that TDM is done for all patients. Only 26.8% participants agreed that TDM is carried out for all drugs. Only 63.2% participants agreed that the TDM is very costly process. Only 38.4% strongly agreed that TDM requires extra time of health care professionals and only 36% participants remain neutral to the perception that TDM is requested by patient rather than health care professionals.

Issues to be Tackled in Developing Countries Related to Drugs

(a) Alternative systems of medicine therapy
(b) Tropical diseases and nutritional deficiencies
(c) Ethnic differences and extrapolation of the normal range
(d) Quality control in drug assays
(e) Quality of medicines and generic formulations

Developing countries face problems like weak health-care structures, limited financial resources, unstable supply and quality of pharmaceuticals, inefficient drug legislation and policy and rising rates of inappropriate self-medication among general public.

Recommendations in Regard to Improve the Situation of Therapeutic Drug Monitoring

- Drug concentrations must be measured under the supervision of clinical trained staff and within the appropriate timeframe in laboratories and subject to quality assays.
- The standard laboratory turnaround time must be less than the dosing interval, nonetheless, because of financial restrains,

these assays are performed in batches and this prolongs the turnaround time.

- The units in which plasma drug concentration are reported are mass and molar mass units. The interpretations of results with these formulas make it easy to repot.
- Different laboratories may vary in standard values and validated target limits therefore it should be stipulated with results to assist physicians for safe as well as effective prescribing.
- All institutions would promote drug monitoring and interpretive services. It would enhance the rational drug prescribing and effective use of drugs. It would also control the excessive use of drugs especially antibiotics.
- Therapeutic drug monitoring must be performed for drugs with narrow therapeutic range e.g., digoxin and antibiotics.
- Special seminars and workshops are recommended to encourage the practice of therapeutic drug monitoring in Pakistan.
- A group of people with ample knowledge of methods of therapeutic drug monitoring should be appointed in every clinical setup to perform therapeutic drug monitoring to increase efficacy of drugs.

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Conflict of Interests

There was no conflict of interests among authors

Annexure

Data Collection Form

Awareness of Therapeutic Drug Monitoring (TDM) in Health Care Professionals

Name:
Age:
Gender: M / F

1. Job in Hospital:

a. Nurse
b. Medical officer
c. House officer
d. Specialist
e. Hospital Pharmacist

1. What is Therapeutic Drug Monitoring (TDM):

a. Measurement of drug concentration in blood
b. Measurement of level of drug toxicity in blood
c. Measurement of patient drug abuse
d. Measurement of required drug dose

2. TDM is indicated when:

a. The prescribed drug has narrow therapeutic index (TI)
b. The consequences of overdosing and underdosing are serious
c. Patients with chronic kidney diseases
d. Both a and b

3. MTC is

a. Minimum concentration required for therapeutic effect
b. Minimum concentration in which toxicity usually occurs
c. Conc. Of drug that produces therapeutic effect
d. Unknown concentration of drug

5. What is MEC

a. Minimum concentration of drug Required for therapeutic effect
b. Maximum dose of drug for therapeutic effect
c. Maximum effective dose
d. Drug of unknown concentration

6. Therapeutic window is defined as

a. Ratio between two effective doses
b. Ratio between MEC and MTC
c. Both
d. none

7. What is trough concentration

a. Lowest concentration of drug in blood stream before next dose
b. Highest concentration of drugs in blood before reaching therapeutic window
c. none of these
d. not specified

8. Peak concentration Is known as

a. Lowest concentration
b. Highest concentration in blood stream
c. Highest and lowest concentration
d. None of these

9. Purpose of TDM:

a. To ensure medication dose is at therapeutic range
b. To avoid or anticipate toxic concentration
c. To monitor unexpected lack of efficacy
d. all of these

10. Have u ever done TDM in your hospital?
a) No
b) Yes
c) Once
d) Twice a month

11. How often do you carry out TDM:
a) Daily
b) 2 or 3 times a week
c) Weekly
d) 2 or 3 times a month
e) Monthly
f) Other

12. The most common recommended method for TDM:
a) HPLC
b) GC
c) Immunoassay

13. From the following list of drugs, which have you carried out TDM on in last 3 months? Please tick all that apply:
a) Cyclosporin
b) Sirolimus
c) Digoxin
d) Phenytoin
e) Tacrolimus
f) Carbamazepine
g) Lithium
h) Phenobarbital
i) Methotrexate
j) Gentamycin
k) Tricyclic antidepressants
l) Other

14. Perceptions regarding TDM:

Perceptions	Strongly Agree	Agree	Neutral	Strongly disagree	Disagree
TDM is done for all patients					
TDM is carried out for all drugs					
The process of TDM is very costly					
TDM requires extra time of health care professional					
TDM is requested by patient rather than health care professional					

15. Practical problems in carrying out TDM are:
a) Lack of resources
b) Financial constraints
c) Overburdened health care professionals
d) Lack of expertise to perform TDM
e) Lack of time

16. How confident do you feel about your ability to understand and interpret the data which you produce:
a) Not confident at all
b) Slightly confident
c) Confident
d) Very confident

17. Source of information:
a) Textbooks
b) Internet
c) Conference
d) Colleagues
e) Web seminar

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