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Role of Therapeutic Drug Monitoring in Medication Safety, Physicians Perception, and Practice

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Patients admitted to the hospital will receive various drugs, each carrying the risk of error. Medication errors concern our healthcare system, especially considering the relatively high number of patients admitted to hospitals. Assuming that each patient receives at least two

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medications twice a day, the likelihood of a medication error is considerable. Therefore, therapeutic drug monitoring (TDM) focuses on measuring blood medication levels and plays a crucial role in medication safety.

Aims: This study aimed to determine the effect of TDM in ensuring the safety of medications in many Taif hospitals. Also, to enhance the safety and quality of drug use and reflect physician perception and practice regarding TDM.

Methodology: A prospective cross-sectional study consisting of questionnaires was conducted to physicians at many of Taif's governmental hospitals between March and May 2021. Questionnaires evaluated three parts: physician demographics, physician perception about TDM, and physician practices regarding TDM. The collected data were processed using the Excel program.

Results: More than 80% of the interviewed physicians agreed that TDM is a tool that can guide the clinician to provide effective and safe drug therapy in the individual patient. Approximately 77% agreed that TDM is a team of decision-making groups. Around 25% of physicians performed TDM weekly, 22% monthly, and 10% daily. The medications that participating physicians ordered TDM were digoxin (30%), carbamazepine (21%), and gentamycin (17%). The participants had a limited understanding of the advantages of TDM in terms of drug safety and welfare.

Conclusion: The number of actual drug errors occurs in the healthcare systems. Therefore, must establishment of TDM in hospitals. Medical administration and physicians must cooperate with the clinical pharmacist. Also, establish workshops for health practitioners to educate them about the role of TDM and pharmacokinetic laboratories in controlling the therapeutic process.

Keywords: Therapeutic drug monitoring; medication safety; physician's knowledge; Doctors perception.

1. INTRODUCTION

Over the last half-century, significant progress has been made in treating various health issues, most notably infectious diseases. Unfortunately, the use of unsuitable medications to treat these conditions has resulted in significant health care problems, including increased morbidity, mortality, and prices and the development of drug resistance in recent years [1,2]. Irrational medication usage in hospitals in developing countries is a serious issue, and little research on how to address it has been published. A possible beginning point is establishing hospital-based Drug and Therapeutics Committees (DTCs) to serve as change agents [3,4]. This was one of the suggestions made during the 1997 International Conference on Improving Use of Medicines (ICIUM) held in Thailand. The advice was made in light of experiences learned from developed countries. More information regarding such committees has been released [5].

Among the additional complications associated with improper drug use include an increase in adverse drug reactions (ADR), medication errors, and the use of relatively unsafe medications [6,7]. In the United States of America, it is estimated that 10.8 % of hospital inpatients suffer from an ADR, costing between US$1.4 billion and US$4 billion annually. Adverse drug reactions are the fourth to the sixth leading cause of mortality [8]. DTC may implement processes aimed at reducing ADRs. Numerous countries currently have DTCs to solve medication selection, procurement, distribution, and usage issues and manage ongoing and developing drug concerns [9]. Most DTCs occur in developed countries, such as Australia, the United States of America, and Europe. In Australia, 92 % had established a hospital therapeutic committee. In contrast, in the United Kingdom, 86 % had established some form of hospital therapeutic committee. In the United States of America, accreditation requires the presence of DTCs or similar committees. They may also be referred to as a Pharmacy and Therapeutics Committee, a Pharmacotherapy Committee, a Formulary Committee, or a Rational Drug Use Committee in various situations [10,11].

TDM is one of the DTCs inside a hospital or primary care clinic responsible for monitoring the clinical use of pharmaceuticals, formulating drug use and administration rules, and maintaining the formulary system. TDM also provides drug-related advice to the medical, nursing, administrative, and pharmacy departments and examines drug usage to detect possible concerns. Furthermore, it is utilized to prevent adverse drug reactions and medication mistakes [12].

TDM is a subfield of clinical chemistry that focuses on the assessment of drug concentrations in the blood. Its primary emphasis is on pharmaceuticals with a limited therapeutic range readily under- or overdosed, such as aminoglycoside antibiotics and antiepileptic medications. The efficacy of these medications is close to the threshold at which they generate severe adverse effects and/or toxicity. Nevertheless, numerous therapeutically regulated medications are prescribed indefinitely. In addition, patients may develop chronic diseases over time, such as heart disease, renal disease, thyroid disease, and liver disease. Therefore, they need monitoring medications. Since a result, TDM may play an important role in medication safety, as it can detect toxicity with any of these medications with a limited therapeutic range [13–15].

Until writing, no study has been done to assess the role of therapeutic drug monitoring in medication safety and assess physicians' knowledge, practice, and opinion towards TDM in Taif city. Therefore, we did this study also to know which drugs require monitoring and enhance the safety and quality of medication use.

2. METHODOLOGY

Prospective cross-sectional research comprising questionnaires was performed to physicians at Taif's governmental hospitals (King Abdul-Aziz Hospital, King Faisal Hospital, Prince Mansour Hospital, and AL-Hada Hospital) between March and May 2021. A convenient technique of sampling was used. Physicians aged between 30 to 60 years were recruited. The verbal informed agreement was acquired, and physicians who refused to participate in the research were excluded.

The data collection approach was a face-to-face interview with the use of a structured questionnaire. The first section of the questionnaire was meant to elicit demographic information about physicians (gender, age, nationality, and Specialty). The questionnaire's second section was aimed to elicit physicians' perceptions about TDM. The final section of the questionnaire was aimed to elicit information on physicians' TDM practices. 'Agree,' 'disagree,' and 'do not know' were used to respond to questions.

The Excel program was used to gather and analyze the data. The descriptive data were reported using frequencies and percentages.

3. RESULTS AND DISCUSSION

3.1 Physician's Demographic Characteristics

One hundred physicians were included in the current study based on their demographic features. More than half (62%) were males compared to (38%) females. Physicians ranged in age from 30 to 60 years. However, 58 % of the participants were under the age of 40, more dominant than 42% were over 40, which means almost participants had a limited understanding of the advantages of TDM. Because this study was conducted in Saudi Arabia, 63% of participants were Saudis compared to 37% were Non-Saudi. The majority of physicians who participated in the research were specialists (30%) and general practitioners (27%) (Table 1).

3.2 Physicians' Perception about TDM

According to physicians' perceptions of TDM, table 2 indicates that more than 80% of physicians interviewed agreed that TDM is a tool that can assist clinicians in providing effective and safe drug therapy to individual patients, and 77% agreed that TDM is a collaborative decision-making group comprised of physicians, clinical pharmacists, nurses, caseworkers, and supervisors. Additionally, roughly 88% of respondents agreed that the clinical pharmacist might play a critical role in guiding TDM collaboration services.

Of the 100 physicians questioned, only 23% agreed that TDM is limited to drug concentration monitoring. In contrast, 57% think otherwise. 86 % of physicians agreed that TDM is necessary for patients with various conditions that impact medication levels. Additionally, most physicians 67 % agreed that TDM is helpful to assess medications with a limited therapeutic index range TDM. By contrast, 9% disagreed. Approximately 44% of physicians agreed that the optimal time to sample blood from patients suspected of drug toxicity is when the symptoms are happening, whereas 41% disagreed (Table 2).

Around the world, about 80% of samples were transmitted to a TDM service. The samples came from a variety of hospital departments and other healthcare facilities. In contrast, this is not the case in Taif hospitals, since the doctors questioned lacked proper understanding and

background about the importance of TDM in drug safety. As a result, most physicians dismiss TDM as a tool that may deliver effective and safe medication to each patient [16,17].

Hospitals and medical facilities strive to offer a tranquil healing environment for patients while also providing thorough medical treatment. However, this carries the risk of medication errors and the chance of other errors and mishaps due to enormous numbers of people continually going in and out each day. As a result, it is critical to construct TDM and pharmacokinetic monitoring labs to provide and assure a safe, confidential, and high-quality healthcare environment for medical personnel and patients [18].

Around 23% of physicians questioned think TDM is used in major organ failure, 21% think TDM is used in low therapeutic index medication, and 19% think TDM is used in therapeutic failure (Table 3). Around 34% of physicians interviewed think that TDM is critical for understanding the pharmacological and pharmacokinetic profiles of the administered drug, and 30% think that TDM is critical for determining the patient's serum or blood drug concentration at the appropriate time after drug administration (Table 4).

As shown in Tables 2-4, participants had a limited understanding of the advantages of TDM in terms of drug safety and welfare, owing to the unavailability of pharmacokinetic labs in all Taif hospitals except Alhada hospital.

A literature review examining medication safety in Australian health care was undertaken in 2002-2008 for the Australian Commission on Safety and Quality in Health Care to build a safer medication system. These commissions are needed for better and safer medication services in Saudi hospitals and healthcare centers [19].

3.3 Physician's Practice on TDM

According to physician practices, around 25% of physicians perform TDM weekly, 22% monthly, and 10% daily (Table 5). The medications that participating physicians ordered TDM in the three months before the study were digoxin (30%), carbamazepine (21%), and gentamycin (17%)(Table 6).

Digoxin, carbamazepine, and antibiotics were the main requested drugs for TDM reported by Leung et al. [20]. However, these medications are acknowledged to be dangerous and have a limited therapeutic index among doctors. This was the primary reason for forcing them to test these medications [21,22].

Approximately 31% of respondents think that gentamicin should be monitored when potential toxicity occurs: if repeated, the sample should not be less than one half-life of the previous sample, while 23% think that gentamicin should be monitored between 24 to 48 hours of treatment. 36% of participants think that digoxin should be monitored when suspected toxicity occurs: if repeated, the sample should not be less than one half-life of the previous sample. In comparison, 20% think it should be monitored for a new patient. 24 % think carbamazepine should be monitored beyond the first two to four weeks of starting medication. 25% of respondents think that phenobarbital should be monitored in the event of suspected toxicity: if repeated, the sample should not be less than one half-life of the previous sample (Table 7).

Table 1. Show demographic data of 100 physicians who participated in the study

Demographic Characteristics		Number	Percent
Gender	Female	38	38 %
	Male	62	62 %
Age	Less than 40	58	58 %
	More than 40	42	42 %
Nationality	Saudi	63	63 %
	Non-Saudi	37	37 %
	Consultant	18	18 %
	Specialist	30	30 %
Specialty	Registrar	25	25 %
	General practitioner	27	27 %

Table 2. Displays physicians' knowledge about TDM by frequency and percentage

Indication	Agree	Disagree	Do not Know
TDM as a tool to provide safe drug therapy	80 (80%)	9 (9%)	11 (11%)
Physicians opinion towards TDM as a teamwork service	77 (77%)	13 (13%)	10 (10%)
Role of clinical pharmacist to guide the TDM team	88 (88%)	4 (4%)	8 (8%)
TDM as only for measuring drug concentration	23 (23%)	57 (57%)	20 (20%)
TDM is essential for patients who have another disease that can affect drug levels	86 (86%)	9 (9%)	5 (5%)
Usefulness of TDM for drugs of narrow therapeutic index range	67 (67%)	9 (9%)	24 (24%)
For patients suspected of symptoms of drug toxicity, the best time to draw the blood specimen is when the symptoms are occurring	44 (44%)	41 (41%)	15 (15%)
TDM role for drugs whose therapeutic effect cannot be readily assessed	50 (50%)	21 (21%)	29 (29%)
Role of TDM for drugs with considerable individual variability in steady-state plasma concentration existing at any given dose	57 (57%)	17 (17%)	26 (26%)
The necessity of TDM when the clinical outcome is unrelated either to dose or to drug plasma concentration	45 (45%)	28 (28%)	27 (27%)

Table 3. Show the opinion of physicians for TDM indication

Indication	Number	Percent
Low therapeutic index	21	21 %
Poorly defined clinical endpoint	6	6 %
Non-compliance to therapy	12	12 %
Therapeutic failure	19	19 %
Drug with saturable metabolism	4	4 %
Wide variation in the drug metabolism.	10	10 %
Major organ failure	23	23 %
Prevention of adverse drug effect	5	5 %

Table 4. Show the importance of TDM service optimizations

Indication	Number	Percent
Measurement of patient’s serum or blood drug concentration must be taken at the appropriate time after drug administration	30	30%
Knowledge of relevant patient’s profiles like demographic data, clinical status, laboratory, and other clinical investigation	19	19%
Knowledge of pharmacological and pharmacokinetic profiles of the administered drug	34	34%
Interpretation of serum drug concentration after consideration of all above information and individualizing drug regimen according to the clinical needs of the patient	17	17%

Doctors were less interested in monitoring therapeutic levels at switching medicines or starting new medications. Because they think they treat people, not medicine serum levels, so they are more concerned with the patient's symptoms than the drug's blood levels.TDM requested for therapy failure and pharmaceutical side effects.

The results revealed that physicians' knowledge of TDM is fair, but further education and workshops are needed to improve physician knowledge. These should include TDM data, target medications, indications, sampling protocols, and anticipated laboratory services. Also, these TDM tests must be included in the standard authorized procedures for case management in the various specialties dealing with TDM drugs. Revision of the laboratory report data is encouraged to urge the physician to seek more TDM, especially with the introduction of medicines. Also, the correct time of TDM sampling should be considered. They may be put on TDM request forms or disseminated as a message to assist physicians inadequate sampling.

Table 5. Show the physician's practices of how often they carry out TDM

Indication	Number	Percent
Daily	10	10%
Two or three times per a week	15	15%
Weekly	25	25%
Two or three times a month	12	12%
Monthly	22	22%
Others	16	16%

Table 6. Show the drugs for which participated physicians requested for TDM in the three months before the survey

Indication	Number	Percent
Lithium	13	13%
Digoxin	30	30%
Phenytoin	15	15%
Carbamazepine	21	21%
Gentamycin	17	17%
Others	4	4%

Table 7. indicate the opinion of participating physicians when some drugs should be monitored

Indication		Frequency	Percent
Gentamicin	As initial monitoring within 24-48 h of therapy	23	23%
	Suspected toxicity: if repeated, should not be less than one half-life of the previous sample	31	31%
	No or inadequate response	16	16%
	After a change in dose regimen	10	10%
	Suspected drug-interaction	20	20%
Indication		Frequency	Percent
Digoxin	As initial monitoring for new patient	20	20%
	Suspected toxicity: if repeated, should not be less than one half-life of the previous sample	36	36%
	No or inadequate response	8	8%
	Suspected non-compliance	6	6%
	Suspected drug-interaction	19	19%
	After a change in dose regimen	11	11%
Indication		Frequency	Percent
	As initial monitoring after 2 – 4 weeks of initiation of therapy	24	24%

Indication		Frequency	Percent
Carbamazepine	Within six h after seizure recurrence	8	8%
	Suspected toxicity: if repeated, should not be less than one half-life of the previous sample	19	19%
	No or inadequate response	5	5%
	Suspected non-compliance	14	14%
	Suspected drug-interaction	11	11%
	After a change in dose regimen	7	7%
	Every 6 – 12 months in stable adults and every 4 – 6 months in stable children	12	12%
Indication		Frequency	Percent
Phenobarbital	As initial monitoring after 2 – 3 weeks of initiation of therapy	20	20%
	Within six h after seizure recurrence	7	7%
	Suspected toxicity: if repeated, should not be less than one half-life of the previous sample	25	25%
	No or inadequate response	3	3%
	Suspected non-compliance	14	14%
	Suspected drug-interaction	12	12%
	After a change in dose regimen	8	8%
	Every 6 – 12 months in stable adults and every 4 – 6 months in stable children	11	11%

4. CONCLUSION

The number of actual drug errors occurs in the healthcare systems. Therefore, must establishment of TDM in hospitals. Utilizing TDM effectively needs a multidisciplinary strategy that incorporates pharmacodynamics, pharmacological and pharmacokinetic methodologies.

Physicians had a limited understanding of the advantages of TDM. Therefore must establish workshops for health practitioners to educate them about the role of TDM.

Medical administration and physicians must cooperate with the clinical pharmacist. In addition, pharmacokinetic laboratories must establish it in all hospitals to control the therapeutic process. Finally, undergraduate medical schools should consider TDM more. This should increase medical graduates' understanding and attitude about TDM.

CONSENT

Informed consent was obtained from all the participants.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Wittich CM, Burkle CM, Lanier WL. Medication Errors: An Overview for Clinicians. Mayo Clin Proc [Internet]. 2014;89(8):1116–25. Available:https://linkinghub.elsevier.com/retrieve/pii/S002561961400439X
2. Bates DW, Slight SP. Medication Errors: What Is Their Impact? Mayo Clin Proc [Internet]. 2014;89(8):1027–9. Available:https://linkinghub.elsevier.com/retrieve/pii/S0025619614005679
3. Sofat R, Cremers S, Ferner RE. Drug and therapeutics committees as guardians of safe and rational medicines use. Br J Clin Pharmacol [Internet]. 2020;86(1):10–2. Available:https://onlinelibrary.wiley.com/doi/10.1111/bcp.14088
4. Fadare JO, Ogunleye O, Obiako R, Orubu S, Enwere O, Ajemigbitse AA, et al. Drug and therapeutics committees in Nigeria: evaluation of scope and functionality. Expert Rev Clin Pharmacol [Internet]. 2018;11(12):1255–62. Available:https://www.tandfonline.com/doi/full/10.1080/17512433.2018.1549488
5. Beran D, Gill G, Yudkin J, Keen H. Third international Conference for Improving Use

of Medicines Informed Strategies, Effective Policies, Lasting Solutions. Irrational Use Diabetes Med Resour Settings. 2011;(Icium):35.

6. Pont L, Alhawassi T, Bajorek B, Krass I. A systematic review of the prevalence and risk factors for adverse drug reactions in the elderly in the acute care setting. Clin Interv Aging [Internet]. 2014 Dec;2079.
Available: http://www.dovepress.com/a-systematic-review-of-the-prevalence-and-risk-factors-for-adverse-dru-peer-reviewed-article-CIA
7. Laatikainen O, Sneck S, Turpeinen M. Medication-related adverse events in health care—what have we learned? A narrative overview of the current knowledge. Eur J Clin Pharmacol [Internet];2021.
Available:https://link.springer.com/10.1007/s00228-021-03213-x
8. Lazarou J, Pomeranz BH, Corey PN. Incidence of Adverse Drug Reactions in Hospitalized Patients. JAMA [Internet]. 1998;279(15):1200.
Available:http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.279.15.1200
9. Alefan Q, Alshareef S, Al-Shatnawi S. Drug and therapeutics committees in Jordanian hospitals: a nation-wide survey of organization, activities, and drug selection procedures. Pharm Pract (Granada) [Internet]. 2019;17(4):1590.
Available:https://www.pharmacypractice.org/index.php/pp/article/view/1590
10. LMW, BROOKS C. Drug and Therapeutics Committees in Australia: expected and actual performance. Br J Clin Pharmacol [Internet]. 1996;42(5):551–7.
Available:http://doi.wiley.com/10.1111/j.1365-2125.1996.tb00048.x
11. Tan EL, Day RO, Brien JE. Perspectives on Drug and Therapeutics Committee policy implementation. Res Soc Adm Pharm [Internet]. 2005;1(4):526–45.
Available:https://linkinghub.elsevier.com/retrieve/pii/S1551741105000951
12. Ates HC, Roberts JA, Lipman J, Cass AEG, Urban GA, Dincer C. On-Site Therapeutic Drug Monitoring. Trends Biotechnol [Internet]. 2020;38(11):1262–77.
Available:https://linkinghub.elsevier.com/retrieve/pii/S0167779920300615
13. Mabilat C, Gros MF, Nicolau D, Mouton JW, Textoris J, Roberts JA, et al. Diagnostic and medical needs for therapeutic drug monitoring of antibiotics. Eur J Clin Microbiol Infect Dis [Internet]. 2020;39(5):791–7.
Available:http://link.springer.com/10.1007/s10096-019-03769-8
14. Patsalos PN, Spencer EP, Berry DJ. Therapeutic Drug Monitoring of Antiepileptic Drugs in Epilepsy: A 2018 Update. Ther Drug Monit [Internet]. 2018;40(5):526–48.
Available:https://journals.lww.com/00007691-201810000-00002
15. Cusumano JA, Klinker KP, Huttner A, Luther MK, Roberts JA, LaPlante KL. Towards precision medicine: Therapeutic drug monitoring–guided dosing of vancomycin and β-lactam antibiotics to maximize effectiveness and minimize toxicity. Am J Heal Pharm [Internet]. 2020;77(14):1104–12.
Available:https://academic.oup.com/ajhp/article/77/14/1104/5857350
16. Therapeutic Drug Monitoring: MedlinePlus Medical Test [Internet].
Available: https://medlineplus.gov/lab-tests/therapeutic-drug-monitoring/
17. Gross AS. Best practice in therapeutic drug monitoring. Br J Clin Pharmacol [Internet]. 1998;46(2):95–9.
Available:https://onlinelibrary.wiley.com/doi/abs/10.1046/j.1365-2125.1998.00770.x
18. Gogtay NJ, Kshirsagar NA, Dalvi SS. Therapeutic drug monitoring in a developing country: an overview. Br J Clin Pharmacol [Internet]. 2001 Sep;52(S1):103–8.
Available:http://doi.wiley.com/10.1046/j.1365-2125.2001.0520s1103.x
19. Roughead EE, Semple SJ. Medication safety in acute care in Australia: where are we now? Part 1: a review of the extent and causes of medication problems 2002–2008. Aust New Zealand Health Policy [Internet]. 2009;6(1):18.
Available:https://anzhealthpolicy.biomedcentral.com/articles/10.1186/1743-8462-6-18
20. Leung D, Ensom MHH, Carr R. Survey of Therapeutic Drug Monitoring Practices in Pediatric Health Care Programs across Canada. Can J Hosp Pharm [Internet]. 72(2):126–32.
Available:http://www.ncbi.nlm.nih.gov/pubmed/31036973
21. Blix HS, Viktil KK, Moger TA, Reikvam A. Drugs with narrow therapeutic index as indicators in the risk management of

hospitalised patients. Pharm Pract (Granada). 2010;8(1):50–5.

22. Yu LX. Quality and bioequivalence standards for narrow therapeutic index drugs. Food Drug Adm [Internet]. 2011;1–37. Available:https://www.fda.gov/downloads/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/abbreviatednewdrugapplicationandagenerics/ucm292676.pdf

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