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Do Healthcare Providers' knowledge associated with Therapeutic drug monitoring services in Duhok-Iraq?

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ABSTRACT

Background and aim: Therapeutic Drug Monitoring (TDM) is an important clinical test for ensuring that an optimal dosage concentration for a patient is maintained. However, many challenges exist that hinder clinicians from performing TDM. The study's objective is to assess the healthcare providers' (HCP) knowledge and attitude of TDM, its availability, and their awareness and importance of this test.

Methodology: In a cross-sectional study, the research setting was Healthcare Provider (HCP) in Duhok Governorate. A survey questionnaire was used for data collection, distributed through Google Forms. The sample of HCP was selected randomly. The study's findings shed light on HCPs' knowledge and attitude about PK/TDM.

Results: Most respondents were between 30 and 50 years old (65.4%). Male responders dominated (71.5%), and 40.8% were pharmacists. Significant association of total knowledge score among different medical degrees (p-value =0.03) and training courses (p value=0.01). Also, 67.6% of the respondents strongly agreed that patient care requires dose adjustment. Other (53.1%) strongly agreed that PK/TDM improves practice.

Conclusion: The study found that the knowledge and attitude of HCP were sufficient. However, some changes must be made to hinder practice more smoothly for HCP, Such as pharmacokinetics (PK) being part of the study and hospitals having special TDM laboratories, which can help enhance patient outcomes.

Keywords: *Therapeutic Drug Monitoring (TDM), Pharmacokinetic (PK), Health Care Practitioners (HCP), Duhok*

INTRODUCTION

Therapeutic Drug Monitoring (TDM) routinely measures plasma drug concentrations. TDM ensures that patients receive optimal dosages within the therapeutic range. (Hiemke et all, 2018). TDM also evaluates drug efficacy and safety using pharmacokinetics, pharmacodynamics, and pharmaceutics. (Vermeire et al. 2020). TDM in Iraq is suboptimal, according to a few research. Hamadi et al. (2015) examined Iraqi hospital physicians' views on pharmacists' role, and the majority of physicians contacted for that study stated

that they rarely engaged with hospital pharmacists. Further, this study advents that drug availability was the main focus of physicians instead of adverse effects, dose, and side effects. The core finding of this study demonstrates that a large majority of physicians were uncomfortable developing and supervising pharmacologic therapy. Unexpectedly, 80.9% of these physicians were also uncomfortable monitoring pharmacotherapeutic outcomes. Confirming the study's findings as mentioned earlier, Iraqi hospitals have poor medication monitoring practices overall.

TDM in Duhok is understudied. This research's preliminary pilot study found that TDM is only performed in private laboratories in Duhok governorate; when this study asked patients about these tests, their level of awareness was low. On the other hand, the healthcare providers' awareness level and understanding of the importance were also unexpectedly low. Abdulkareem et al. (2016) examined physician-prescribed drugs at Duhok private hospitals. The research found significant gaps in Adverse Drug Reaction (ADR) monitoring.

Barriers to TDM inform pharmaceutical efficacy and safety. Unfortunately, many impediments prevent clinical TDM practice. The first obstacle is patient-specific. For instance, troughs may develop outside the clinical context, and non-compliance of the patient disrupts TDM timing (Abdulla et al. 2021).

Additional Barriers to TDM include lack of experience, non-existent pharmacokinetic data to influence dosage optimization decisions, low remuneration for TDM services, and the need for more technology tools to improve the TDM process, such as dose optimization software (Nigam et al. 2021). This study evaluates TDM services and expertise among Duhok's HCP.

METHODOLOGY

The cross-sectional study examined Health Care Practitioners HCP's TDM knowledge and attitudes through a Survey Questionnaire in Duhok Governorate. (Tappen 2022).

Alrabiah et al. inspired the questionnaire (2021); the researcher developed a TDM knowledge, attitude, awareness, and importance questionnaire with the help of 23 HCP in Duhok. The questionnaire contained a demographic part, general information, and participants, knowledge part, which included questions regarding general knowledge of PK/TDM, as shown in Table 3.5. it also contained an Attitude section asking HCP about their attitude toward the subject, as shown in Table 3.8.

The University of Duhok, College of Pharmacy, and Duhok Directorate General of Health ethics committee gave us ethical approvals.

After validation and reliability, the developed questionnaire was converted to google Forms and sent to 310 HCP; the survey returns were 57.7% (n=179). 179 HCP participated, including physicians, pharmacists, nurses, and laboratory staff, from October 2021 through September 2022.

The participants were informed about the aspect of the research, and the researcher obtained HCP approval to participate. The survey was unanimous. As an observational study, this did not impair psychological, physiological, legal, financial, or social well-being. Overall, the research had no interventions.

Data were analyzed using SPSS 26. Data were analyzed as a single cohort and by demographics such as age, practice type, specialty, gender, and practice setting. Data type and distribution normalcy determined the statistical test. Independent T-tests and one-way ANOVA compared continuous and regularly distributed variables.

RESULTS

Demographic data

Table 3.1 presents that 65.4% (n=117) of respondents were middle-aged, 30–50 years old. Male responders dominated at 71.5% (n=128), and 40.8% (n=73) were pharmacists, followed by consultants at 34.1% (n=61).

TABLE 3.1: Responder's Age, Gender & Medical Profession

		Frequency	Percent
Age (Years)	<30	48	26.8
	30-50	117	65.4
	>50	14	7.8
Gender	Male	128	71.5
	Female	51	28.5
Medical Profession	Pharmacist	73	40.8
	Consultant	61	34.1
	Resident	26	14.5
	General Practitioner	12	6.7
	Nurse	4	2.2
	Laboratory personal	3	1.7
	Total	179	100

Respondents' Specialties

Table 3.2 shows that the most reported participants are pharmacists (40.7% n=73). Laboratory personnel is the fewest respondents, 1.7% (n=3).

TABLE 3.2: Respondents' Specialties

		Count	%
Specialty	Physician	99	55.3
	Pharmacist	73	40.8
	Laboratory personal	3	1.7
	Nurse	4	2.2
	Total	179	100

Respondents' University of graduation, experience, Pharmacokinetic Course & Practice Location

A significant demographic characteristic allowed the researcher to establish how TDM knowledge and attitude varied by HCP study location. In table 3.3, 77.7% (n=139) of the respondents graduated from Kurdistan Region (KR) Universities. 32.4% (n = 58) had five to ten years of experience. Unexpectedly, many respondents 46.4% (n=83) did not take pharmacokinetic courses. 87.7% (n = 157) of responders practiced in the Directorate General of Health (DoH) Duhok in different hospitals and specialized centers.

TABLE 3.3: Respondents' University of graduation, experience, Pharmacokinetic Course & Practice Location

		Frequency	Percent
University of graduation	KR universities	139	77.7
	Iraq universities	32	17.9
	outside Country	8	4.5
Years of practice	<5	41	22.9
	5-10	58	32.4
	>10-20	54	30.2
	>20	26	14.5

Have you taken the pharmacokinetic course?	No	83	46.4
	Undergraduate	57	31.8
	Postgraduate	18	10.1
	CME	21	11.7
Where do you practice now?	Universities of Iraq	5	2.8
	Universities of Kurdistan	17	9.5
	DoH	157	87.7
Total		179	100

Knowledge of PK/TDM

Table 3.4 shows that 55.3% (n = 99) responded that maximal drug concentration was reached after the second dose. PK/TDM was not recommended for Ceftriaxone 58.1% (n = 104).

TABLE 3.4: Knowledge of PK/TDM

No			Frequency	%
1	TDM should be used when ethnic differences are suspected to influence drug response	Yes (R)	94	52.5
		No	85	47.5
2	TDM must measure the concentration of the drug after the first dose	Yes	130	72.6
		No(R)	49	27.4
3	TDM services measure the total concentration of the drug (binding + free)	Yes(R)	90	50.3
		No	89	49.7
4	The maximum concentration of the drug is achieved after the second dose	Yes	80	44.7
		No(R)	99	55.3
5	The maximum concentration is measured to ensure the safety of the drug	Yes(R)	118	65.9
		No	61	34.1
6	Does Ceftriaxone require TDM service?	Yes	75	41.9
		No(R)	104	58.1
7	Does Lidocaine require TDM service?	Yes(R)	80	44.7
		No	99	55.3
8	Does Valproic acid require TDM service?	Yes(R)	145	81.0
		No	34	19.0
9	Does Digoxin require TDM service?	Yes(R)	147	82.1
		No	32	19.0
10	Does Gentamycin drop require TDM service?	Yes	62	17.9
		No(R)	117	65.4
11	Does Phenytoin require TDM service?	Yes(R)	153	85.5
		No	26	14.5
12	Does Tacrolimus require TDM service?	Yes(R)	110	61.5
		No	69	38.5
13	Does Cyclosporine require TDM service?	Yes(R)	129	72.1
		No	50	27.9
14	Does Amlodipine require TDM service?	Yes	45	25.1
		No(R)	134	74.9
15	Does Vancomycin require TDM service?	Yes(R)	115	64.2
		No	64	35.8
	Total		179	100

(R) Right answer

Total knowledge score

This study indicated a score for PK/DM knowledge. In such a manner, responders' correct answers were scores of 1; otherwise, a score of 0 was given. The final score ranged from 0 to 15, with a higher score indicating higher knowledge and vice versa. This study used the median spit method to determine the cut for adequate and inadequate knowledge. The median was 9, meaning that a score above nine was considered sufficient knowledge, while a score equal to below nine was regarded as inadequate knowledge. The findings showed that the majority of respondents, 67% (n = 120), had adequate knowledge, while 33% (n = 59) had inadequate knowledge (See Table 3.5)

TABLE 3.5: Total knowledge scores

	Frequency	Percent
Adequate Knowledge	120	67.0
Inadequate Knowledge	59	33.0
Total	179	100.0

Median split for knowledge scores

Knowledge of Pharmacokinetics and Therapeutic Drug Monitoring (PK/TDM)

As shown in table 3.6 Significant association of total knowledge score about PK/TDM among different medical professions (p-value =0.03) was reported. It is also clear in training courses (p-value=0.01).

TABLE 3.6: Total knowledge scores (mean ± SD) among demographic data of HCP.

		N	%	Mean±SD	Sig.
Age	<30	48	26.8	8.46±3.073	0.31
	30-50	117	65.4	9.16±2.619	
	>50	14	7.8	8.71±2.400	
Gender	Male	128	71.5	9.05±2.913	0.4
	Female	51	28.5	8.67±2.233	
Medical profession	Consultant	61	34.1	9.51±2.285	0.03
	GP	12	6.7	7.42±4.562	
	Resident	26	14.5	9.54±2.213	
	Pharmacist	73	40.8	8.38±2.701	
	Laboratory personal	3	1.7	9.67±3.055	
	Nurse	4	2.2	10.50±3.317	
Years of practice	<5	41	22.9	8±3.471	0.08
	5-10	58	32.4	9.41±2.464	
	>10-20	54	30.2	9.09±2.301	
	>20	26	14.5	9.04±2.63	
Specialty	Physician	99	55.3	8.82±3.02	0.36
	Pharmacist	73	40.8	8.38±2.701	
	Laboratory personal	3	1.7	9.67±3.055	
	Nurse	4	2.2	10.50±3.317	
Training	No	83	46.4	8.81±2.516	0.01
	Undergraduate	57	31.8	9.39±2.274	
	Postgraduate	18	10.1	9.44±2.121	
	CME	21	11.7	8.03±3.947	
Practice Location	Universities of Iraq	5	2.8	9.4±2.302	0.71
	Universities of Kurdistan	17	9.5	8.65±3.061	

	DoH	157	87.7	8.98±2.731	
	Total	179	100.0	8.94±2.736	

Comparisons for Knowledge across Course/Training in PK/TDM

The findings showed significant differences in knowledge of PK/TDM across clinicians based on taking a course or training during their study ($p < 0.05$). Post-hoc analysis revealed that clinicians who undertook training in PK/TDM undergraduate (M = 10.0, SD = 2.23) and postgraduate (M = 10.44, SD = 1.97) had significantly higher total PK/TDM knowledge than those who did not complete any course (M = .50, SD = 2.15) ($P < 0.05$). There was no difference in PK/TDM knowledge between those who took a course in postgraduate and undergraduate and those who took a course in CME ($p > 0.05$). Table 3.7 presents detailed summaries of these findings.

TABLE 3.7: Comparisons for Knowledge across Course/Training in PK/TDM

(I) Course or training in PK/ TDM during your study	(J) Course or training in PK/ TDM during your study	Mean Difference (I-J)	Sig.
No	Undergraduate	-1.49398	0.001*
	Postgraduate	-1.93842	0.005*
	CME	-0.63683	0.644
Undergraduate	No	1.49398	0.001*
	Postgraduate	-0.44444	0.881
	CME	0.85714	0.433
Postgraduate	No	1.93842	0.005*
	Undergraduate	0.44444	0.881
	CME	1.30159	0.266
CME	No	0.63683	0.644
	Undergraduate	-0.85714	0.433
	Postgraduate	-1.30159	0.266

Post hoc, The mean difference is significant at $p < 0.05$

Attitudes towards PK/TDM Service

Six items are measuring attitudes about PK/TDM. Whether hospitals need TDM facilities, 66.5% (n=119) strongly agreed. 67.6% (n = 121) of the respondents strongly agreed that patient care requires dose adjustment. 53.1% (n = 95) strongly agreed that PK and TDM improve practice. Table 3.8 show the details.

TABLE 3.8: Respondents' Attitudes toward PK/TDM

			Frequency	%
1	Hospitals need TDM facilities and labs	Strongly Disagree	0	0.0
		Disagree	4	2.2
		Neutral	7	3.9
		Agree	49	27.4
		Strongly Agree	119	66.5
2	TDM and PK enhance the efficacy of medications	Strongly Disagree	0	0.0
		Disagree	7	3.9
		Neutral	18	10.1
		Agree	74	41.3

		Strongly Agree	80	44.7
3	Adjusting dose is important for patient care	Strongly Disagree	0	0.0
		Disagree	0	0.0
		Neutral	5	2.8
		Agree	53	29.6
		Strongly Agree	121	67.6
4	TDM and PK are important in improving practice	Strongly Disagree	0	0.0
		Disagree	2	1.1
		Neutral	8	4.5
		Agree	74	41.3
		Strongly Agree	95	53.1
5	Physicians need to apply PK principles when administering medications with a narrow therapeutic index	Strongly Disagree	0	0.0
		Disagree	4	2.2
		Neutral	14	7.8
		Agree	40	22.3
		Strongly Agree	121	67.6
6	TDM/PK Individualize Drug therapy	Strongly Disagree	0	0.0
		Disagree	1	0.6
		Neutral	21	11.7
		Agree	81	45.3
		Strongly Agree	76	42.5
	Total		179	100

Total attitude score among HCP

The study also scored total attitudes of HCP toward TDM computed by adding scores for six items, ranging from 5 to 30, with higher scores indicating favorable attitudes and lower scores indicating poor attitudes toward TDM. The mean score for attitudes toward PK/TDM was 26.81 (SD = 2.84), meaning highly favorable attitudes. Using the median split method, the study found that most participants, 56.4% (n = 101), had adequate attitudes (See Table 3.9).

TABLE 3.9: Attitude towards PK/TDM

	Frequency	Percent
Adequate Attitude	101	56.4
Inadequate Attitude	78	43.6
Total	179	100.0

Median Split

DISCUSSION

Knowledge of PK/TDMThe HCP's understanding of PK/TDM was good. Other research has found high PK/TDM awareness levels, notably regarding drug concentration monitoring reasons and conditions (Choi et al. 2019; Leung et al. 2019). PK/TDM measures blood, serum, or plasma drug concentrations to establish acceptable target ranges. While it is impossible to assess medicine concentrations at the site of action, blood or plasma concentrations can better predict undesirable or desired effects than dose. Concentration measures can determine drug exposure for some treatments, especially if there is a sensitive or straightforward technique to assess its impact (Choi et al. 2019). PK/TDM is recommended in cases of large inter-individual dose and effect variability, such as

pharmacokinetic variance, which makes customized drug dosing difficult. In this study, most HCP suggested TDM when ethnicity may affect drug response. Hassan et al. found that participants understood the causes for PK/TDM (2022). Many factors motivate PK/TDM. Alomi et al. (2019) say PK/TDM improves drug efficacy and reduces toxicity. PK/TDM aid diagnosis. Regular TDM is not advised, but it should be done when clinically relevant, which needs knowledge of toxicity, dose, and monitoring (Hassan et al. 2022). If a clinical symptom cannot be identified, PK/TDM can detect toxicity. TDM prevents toxicity. After dose adjustments, especially at a steady state, PK/TDM should be done. PK/TDM can also evaluate compliance, detect undertreatment, and diagnose failed treatment to assess if a drug is ineffective, if side effects mirror the underlying ailment, or if there is non-compliance (Leung et al. 2019). Most HCP took PK/TDM courses, which may explain their PK/TDM knowledge. Most respondents had at least five years of experience, which may demonstrate their strong PK/TDM understanding. Previous research found beneficial relationships between clinical experience and PK/TDM expertise. Participants also knew when to perform PK/TDM. This matches Shawahna et al (2022). Samples should be taken at a steady state. Usually, 4-5 half-lives after therapy begin unless TDM is employed to predict toxicity. The concentration of medication at receptors and plasma is usually proportional in a steady state. In patients with weak metabolism, medicines with extended half-life must be monitored before reaching a steady state to prevent toxicity after the first few doses (Shawahna et al. 2022). Early monitoring during the loading phase uses plasma concentration to assess dosage. As medication concentration changes throughout the dosing period, the sample must be taken before the following dose (pre-dose concentration). Samples can be taken during dosing for medicines with long half-lives. Distribution and absorption rate affect the sample collection schedule. Patients are usually sampled to detect peak medication concentration for detection of toxicity when they have specified symptoms (Zhu et al. 2017). Most HCP didn't know PK/TDM timing. Most HCP suggested measuring medication concentration after the first doses. Alrabiah et al. (2021) found acceptable TDM timing information at a steady state. TDM measures medication efficacy, compliance, drug-drug interactions, and toxicity. Plasma concentrations alone can be relevant in several situations (Methaneethorn 2018). Low plasma levels may indicate under-treatment or non-compliance. Poor compliance may be suggested if a patient was prescribed a dose unrelated to the measured low concentration or if the initial measurement indicated that the plasma concentration needed to be higher for the current dose. All medications, especially those with a narrow therapeutic index, require the clinician to personalize dosage. TDM helps alter dosages, too (Shaikh et al. 2018). Zhang et al. found that many practitioners understood the role of PK/TDM in medication safety (2021). Most responders took PK/TDM courses, which may explain these results. Routine monitoring is not advised for all drugs because TDM should only be done when clinically useful. TDM is only advised to prevent toxicity or graft rejection. TDM qualifications (Firman et al. 2022). These criteria include a tight therapeutic range, significant pharmacokinetic fluctuation, a significant correlation between clinical effects and plasma concentration, an established concentration, and a cost-effective drug assay. Digoxin, valpric avid, and carbamazepine (Firman et al. 2022). This study found some TDM medication knowledge gaps, especially in Ceftriaxone. Most respondents knew PK/TDM medicines.

Attitudes towards PK/TDM

Hassan et al. found that respondents exhibited acceptable PK/TDM attitudes (2022). Respondents stressed the following points; the importance of dose adjustment in improving patient care. PK/TDM role in improving clinical practice. Applying PK principles when administering medications with a narrow therapeutic index is necessary. The need for hospitals to have TDM laboratories and facilities, TDM's role in improving medication efficiency, also its role in individualizing medication therapy (Hassan et al. 2022; Shawahna et al. 2022). In intensive care patients, medication response might vary greatly. Monitoring and sustaining

drug dose modification improves treatment outcomes, especially in patients with organ failure like kidney or liver failure, by linking pharmacokinetic data to the therapeutic dose (Alomi et al. 2019). TDM reduces toxicity from incorrect drug dosages, improving drug therapy safety and efficacy. (Leung et al., 2019). Most practitioners in this study believed dose modification improved patient care. Most practitioners surveyed took PK/TDM courses, which may explain these findings. Most responders had five years of experience. Most responders agreed that PK/TDM improves clinical practice. TDM is a critical patient safety factor (Campbell et al. 2017; Choi et al. 2019). PK/TDM interprets drug concentrations based on the patient, not the desired therapeutic range. A patient with a slightly lower anticonvulsant medicine concentration but no seizures does not need to increase the dosage. PK/TDM improves clinical practice by improving patient compliance, identifying therapy failure, and patient safety. Low blood drug concentrations may indicate non-compliance. PK/TDM can distinguish between ineffective treatment and side effects mirroring the primary condition (Choi et al. 2019). TDM improves clinical practice and patient outcomes. Most practitioners in this survey took a PK/TDM course, indicating positive views on its usefulness in clinical practice. Most respondents reported five years of experience. PK principles are also needed when delivering narrow therapeutic index drugs. The research found similar results (Nigam et al. 2021; Zhang et al. 2021). Even tiny dose increases of narrow therapeutic index drugs might cause harm. PK/TDM optimizes treatment when therapeutic/toxic effects are closely related to blood drug concentrations (Nigam et al. 2021). Medication concentrations determine patient compliance and toxicity. Clinical conditions may require medication modifications if levels are outside the therapeutic interval. Adjustments for other drugs that may affect whole blood or serum concentrations and diminish efficacy or increase toxicity may also benefit TDM. Plasma concentration and therapeutic index are significant in determining pharmaceutical therapy, although they are not the only criterion. PK/TDM emphasizes patient treatment over therapeutic levels (Nigam et al. 2021). Drug concentrations are only clinically meaningful if practitioners time samples correctly, according to Firman et al. (2022). (Guo et al. 2019). Most respondents supported PK/TDM for narrow therapeutic interval medicines. This study supported Leung et al. findings that hospitals need PK/TDM laboratories and facilities (2019). Drug assay facilities measure blood drug concentrations and compare them to therapeutic ranges (Hassan et al., 2022). TDM's laboratory analysis, which establishes pharmacokinetic parameters, is often overlooked (Hunt et al. 2021). Most practitioners agreed that hospitals need PK/TDM laboratories and facilities. TDM also improved drug efficacy, supporting studies by (Leung et al. 2019; Methaneethorn 2018). PK/TDM monitors blood medication concentrations to inform clinical action to enhance therapeutic efficacy and safety. Most drugs may be dosed without additional testing, but others, especially those with substantial pharmacokinetic variability, are difficult to dose without serious side effects. PK/TDM helps clinicians find the most effective dose. PK/TDM helps narrow therapeutic index drugs achieve clinical results safely (Methaneethorn 2018). Preventing over- and underdosing makes TDM more cost-effective. Most agree that PK/TDM boosts drug efficacy (Zhu et al. 2017). According to Firman et al., PK/TDM is crucial to individualizing pharmaceutical therapy (2022). PK/TDM has altered medication therapy by identifying the origins of drug response and disposition diversity, which helps individualize prescription dosages. PK/TDM gives information for personalized drug dosage to maintain medication concentrations within the specified range (Zhang et al. 2021). Most responders agreed that PK/TDM enhances individualized drug therapy.

Conclusion and recommendations

The study indicated that the Knowledge and Attitude of HCP in Duhok are sufficient towards TDM. Some changes need to be made for the TDM to be more efficient such as PK being part of the curriculum of study. Also, hospitals in the Public and private sectors adapt to new Facilities for TDM services.

Future studies should examine PK/TDM procedures using observational data instead of self-report data for more reliable results. Studies must watch clinicians in their practice setting to accurately measure physician adoption of PK/TDM techniques.

Authors' contributions

All authors have made substantial contributions to the conception of the study, drafting the article, and final approval of the version to be submitted. OQ, and DA conceived and designed the study. OQ did the electronic search for the relevant articles and drafted the manuscript. DA analyzed the data. OQ and DA revised and edited the manuscript. OQ and DA prepared the manuscript for publication. All authors have read and approved the final submitted manuscript.

Informed consent

Informed consent was obtained from all individual participants included in the study. All patients were informed of their rights to reject sharing in this study. If the patients accepted to share in the study, then they would be asked to agree verbally before starting the questionnaire.

Availability of data and material

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Competing interest

The author declare that they have no competing interests

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