ORIGINAL ARTICLE

Knowledge and Attitude towards Therapeutic Drug Monitoring Practices among physicians in Arar, Saudi Arabia

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ABSTRACT

Aim: The aim of this study was to evaluate knowledge and attitude towards Therapeutic Drug Monitoring (TDM) Practices among physicians in Arar, Saudi Arabia

Methods: the study was conducted through a cross sectional descriptive electronic survey. The questionnaire collected the demographic data of the participants. Also true and false questions were designed to evaluate the awareness of the participants about TDM drugs, indications of TDM, and main obstacles against proper application of TDM in Arar. Also participants were asked about their main source of knowledge about TDM.

Results: 254 percipients had responded to the questionnaire. Digitalis, theophylline, carbamazepine, vancomycin, and imipramine were the most commonly known by doctors as TDM drugs. Regarding the awareness of the participants about the indication of TDM, suspected therapeutic failure was the commonest indication known by the physicians enrolled in the study 212(83.5%), followed by cases with clinical or laboratory manifestations suspecting hepatic or renal affection under the effect of the prescribed medications 171(67.3%). There was a significantly higher awareness about the TDM drugs and indications of TDM among the junior staff members as well as staff with experience less than 10 years. Lacking of the proper laboratory reports and guiding recommendation was the most important point limiting their requesting for TDM. [184 (72.4%)]. While the postgraduate studies were the commonest source of knowledge about TDM [154(62.9%)].

Conclusion: Awareness about TDM among Doctors in Arar is fairly good. However, more work is required to improve the awareness and maximize the clinical benefit of TDM laboratory reports data.

Keywords: Therapeutic drugs monitoring, Carbamazepine, digitalis, theophylline, Awareness, Attitude, Arar

INTRODUCTION

Therapeutic response to the same drug dosage. laboratory measurement of a chemical parameter that, with appropriate medical interpretation, will directly influence drug prescribing procedures[1,2]. TDM is based on conscious monitoring of both pharmacokinetics and pharmacodynamics to get the best therapeutic benefit of any therapeutic agent within the minimal dosage with the least expected side effects and toxicities specially in the vulnerable groups as hepatic, renal, and cardiac patients as well as pregnant ladies and children[3-5].

The first application of TDM was in 19606 as application of mathematical modeling to control the therapeutic levels of the drugs and expect the clinical outcome. Ten years later, clinical pharmacokinetics started to be a separate entity of pharmaceutical sciences[3]. The goal of TDM is to tailor the therapeutic regimens for each patient for optimal therapeutic benefit. Clinically, TDM can measure drug concentrations in the different biological samples with meticulous interpretation of these concentrations in parallel to the available clinical parameters which should be included in TDM laboratory request form[6]. This interpretation is mainly based on the skills of well-trained clinical pharmacists and pharmacologists who can use the predesigned charts of each drug to give the proper advice to the physician who requested the assay[7].

Digoxin was one of the first drugs which as markedly requested by TDM due to its narrow therapeutic indices as well as cumulative toxic effects. In the 1970s, curves were constructed for digoxin proper therapeutic and toxic levels in the different vulnerable groups on digoxin therapy[8]. Later on other drugs were included in the list as phenytoin, lithium, and theophylline[9,10]. The improved awareness about drug concentration/response relationship, the clinical pharmacokinetic monitoring was welcomed by big sectors of physicians in different specialties world-wide. This encouraged wide range of computerized analytical technology involved in TDM[11]. With the era of personalized medicine based on pharmacogenetic and pharmacogenomic research, TDM becomes compulsory practice in a lot of the well-established international healthcare systems with the new understand of the basics of the human genome[12,13]. The newly advanced gene chip technology was extensively applied in the era of gene-based personalized medicine and TDM research studies[14,15].

Arar is the capital of the Northern Border region of Saudi Arabia. The governmental healthcare services are provided in Arar through three two general hospitals in the medical tower and Prince Abdulaziz Bin Musaad Hospital in addition to specialized four hospitals as Prince Abdullah Bin Musaed Cardiac Centre, Arar Maternity and Children Hospital, Convalescent and Medical Rehabilitation Hospital, and Mental Health Hospital. Primary health care services are supplied through multiple primary healthcare centers which are distributed all over the different regions in Arar. The governmental healthcare services in Arar are supplied through around 500 physicians. TDM service is

provided through a central well-equipped regional laboratory. The current study was conducted to study the level of awareness and attitude among the healthcare staff in Arar towards 'TDM' in terms of their genders, ages, years of experience, and specialties. Also the study aimed to highlight the main obstacles against proper use of TDM in Arar.

MATERIAL AND METHODS

The study design was approved by the bioethics committee of Northern Border University (Decision 6/41/H). The study was conducted through cross sectional descriptive, electronic questionnaire based survey. The targeted group was the physicians working in the governmental health facilities in Arar in the primary as well as the secondary healthcare levels. The questionnaire was delivered as a link to a google form containing the questionnaire. The participants were enrolled voluntarily in the study after reading the aim of the study. No data regarding the identity of the participants were collected.

The questionnaire was designed of 4 sections. The first part was designed to collect data regarding place of work, gender, years of experience and positions. The second part includes questions related to their own experience with TDM and their awareness about medications involved in TDM and indications for requesting TDM for the patients maintained on the medications of interest through true and false questions. The third section was mainly deigned to cover the obstacles against the proper practice of TDM. The last section collected about the main source of the participants' knowledge about TDM. Participants have received no incentives for completing of the survey questions. The study questions were validated by department of pharmacology and toxicology in Northern Border University as well as the staff of the toxicology unit in the regional laboratory.

Data Analysis: The total number of physician working in the governmental health facilities in Arar are 500 doctors, so the minimal number of participants for validation of the data was estimated to be 217 participants. Chi Square and fisher exact tests were used to compare the awareness scores among the different participants group whenever appropriate. All statistical analyses were conducted by graph pad prism5. Significance was considered with p-value <0.05.

RESULTS

The study was conducted through electronic questionnaire. 254 physicians have submitted completed answers to all questionnaire questions. The demographic data of the participants are shown in table 1. The participants from the secondary health care service level were the majority of the physician enrolled in the study 219(86.22%). Female represented 133(52.36%) women of the participants.

Table 1: Data regarding the place of work, gender, medical license, years of experience and specialties of doctors enrolled

Participants' Data	No	%
Place of work		
Medical Tower	59	23.23
Prince Abdulaziz Bin Musaad Hospital	47	18.50
Arar Maternity and Children Hospital	65	25.59
Prince Abdullah Bin Musaed Cardiac Centre	21	8.27
Convalescent and Medical Rehabilitation Hospital	8	3.15
Mental Health Hospital	19	7.48
Primary Health-Care Centers	35	13.78
Gender		
Male	121	47.64
Females	133	52.36
Position		
Consultant	47	18.50
Senior registrar	29	11.42
Registrar	82	32.28
Resident	58	22.83
general practitioner	13	5.12
Interns	25	9.84
Years of Experience		
<2 years	41	16.14
2-5 years	39	15.35
6-10 years	49	19.29
11-15 years	73	28.74
>15 years	52	20.47
Specialties		
General Medicine	27	10.63
Chest medicine	14	5.51
Cardiology	21	8.27
Pediatrics	36	14.17
Obstetrics and gynecology	30	11.81
General surgery	17	6.69
Surgery subspecialties	25	9.84
Family medicine	35	13.78
Emergency medicine	16	6.30
ENT	5	1.97
anesthetist and intensivists	12	4.72
Others	16	6.30
Totals	254	100

Regarding to the participants, own experience with TDM, 144(56.69%) reported that they have requested TDM investigations. Digitalis, theophylline, carbamazepine, vancomycin, and imipramine was the most commonly requested [requested by 21(8.3%), 15(5.9%), 12(4.7%), 10(3.9%), and 10(3.9%) physicians respectively.

Regarding to the awareness questions about the types of medications which are mainly targeted by TDM investigations. Digitalis, theophylline, and carbamazepine were the most commonly reported by the participants (Table 2).

There was a significant difference in the reported numbers of medications requesting TDM. Higher number of drugs of interest were identified by the junior staff members as well as staff with experience less than 10 years (p-values 0.0002 and <0.0001 respectively) (Table 3).

Regarding the awareness of the participants about the indication of TDM, suspected therapeutic failure was the commonest indication known by the physicians enrolled in the study 212(83.5%), followed by cases with clinical or laboratory manifestations suspecting hepatic or renal affection under the effect of the prescribed medications 171(67.3%) as shown in table 4.

There was significantly higher numbers of indications reported by participants who were junior staff and with years of experience less than 10 years (Table 5).

Regarding the numbers of obstacles which limit application of TDM in Arar according to the participants' points of views, participants reported that lack of the proper laboratory reports with guiding recommendation was the most important point limiting their requesting for TDM. 184 (72.4%) followed by lack of awareness about the proper timing of sampling and sampling guideline for TDM 173(68.1%) (Table 6).

Regarding the main source of knowledge about TDM among the physician enrolled in the current study, Postgraduate studies were the commonest source of knowledge about TDM 154(62.9%), followed by continuous medical education lectures 55(21.6%), undergraduate studies 34(13.4%) and the internet medical website were only reported by 11 participants (4.3%)

Table 2: Awareness about the drugs targeted by TDM assays by participants enrolled in the study

Drugs	n	%
Antibiotics		
Amikacin	75	29.5
Tobramycin	96	37.8
Vancomycin	102	40.2
Antiepileptics		
Carbamazepine	176	69.3
Phenobarbital	152	59.8
Phenytoin	132	52.0
Valproic acid	127	50.0
Antipsychotics, antidepressants		
Clozapine	67	26.4
Imipramine	89	35.0
Lithium	127	50.0
Immunosuppressants		
Cyclosporine	146	57.5
Antiarrhythmic		
Digoxin	182	71.7
Disopyramide	84	33.1
Lidocaine	69	27.2
Procainamide	87	34.3
Propranolol	111	43.7
Quinidine	110	43.3
Others		
Acetaminophen	56	22.0
Theophylline/aminophylline	167	65.7
Salicylates	47	18.5

Table 3: Effect of participants, gender, clinical positions and clinical years of experience on Awareness about the drugs targeted by TDM assays by participants enrolled in the study. P-values were estimated by Chi square test. *** means p-vale <0.001 and **** means p-vale <0.0001. Seniors means consultants and senior registrar, while juniors include registrar, residents, general practitioners and interns.

Variables		Totals	Number of reported medications indicating TDM				X^2
			<5 drugs	5 to 10 drugs	10 to 15 drugs	>15 drugs	P-value
Gender							
Male	Number	121	23	55	34	9	2.362, 3
	%	100	19.01	19.01	19.01	19.01	0.5007
Females	Number	133	26	59	31	17	
	%	100	17.29	17.29	17.29	17.29	
Positions							
Seniors	Number	76	9	49	16	2	19.39, 3
	%	100	11.84	64.47	21.05	2.63	0.0002***
juniors	Number	178	40	65	49	24	
	%	100	22.47	36.52	27.53	13.48	
Years of Experience							
Up to 10 y	Number	129	20	41	47	21	39.54, 3
	%	100	15.50	31.78	36.43	16.28	< 0.0001****
>10 y	Number	125	29	73	18	5	
	%	100	23.20	58.40	14.40	4.00	
Totals	Number	254	49	114	65	26	
	%	100	19.29	44.88	25.59	10.24	

Table 4. Awareness about the indications for requesting TDM assays by participants enrolled in the study

variables		Total	Onset of treatment	Shift from a medication to another	Suspected therapeutic failure	Liver and/or kidney impairment
Gender						
Male	Number	121	21	32	102	92
	%	100	17.36	26.45	84.30	76.03
Females	Number	133	25	31	112	79
	%	100	18.80	23.31	84.21	59.40
Positions						
Seniors	Number	76	18	21	59	50
	%	100	23.68	27.63	77.63	65.79
Juniors	Number	178	28	42	155	121
	%	100	15.73	23.60	87.08	67.98

Years of experience						
Up to 10 years	Number	129	16	15	48	42
	%	100	12.40	11.63	37.21	32.56
>10 years	Number	125	30	48	166	129
	%	100	24.00	38.40	132.80	103.20
Totals	Number	254	46	63	214	171
	%	100	18.11	24.80	84.25	67.32

Table 5. Effect of participants, gender, clinical positions and clinical years of experience on Awareness about the indications for requesting TDM assays by participants enrolled in the study. P-values are identified by Fisher exact test. ** means p-vale <0.01. Seniors means consultants and senior registrar, while juniors include registrar, residents, general practitioners and interns.

Variables		Total	Number of reported indications		p-value
			1 or 2 indications	> 2 indications	
Gender					
Male	Number	121	121	66	0.9
	%	100	100	54.55	
Females	Number	133	133	71	
	%	100	100	53.38	
Positions					
Senior	Number	76	51	25	0.0062**
	%	100	67.11	32.89	
Junior	Number	178	86	92	
	%	100	48.31	51.69	
Years of experience					
Up to 10 y	Number	129	81	48	0.0055**
	%	100	62.79	37.21	
>10	Number	125	56	69	
	%	100	44.80	55.20	
Totals	Number	254	137	117	
	%	100	53.94	46.06	

Table 6. Obstacles against proper used of TDM according to the participants' points of views.

Obstacles against TDM	Number of participants reported obstacle	%
Expected limited clinical value	126	49.6
Unavailability in the hospital or the medical center	97	38.2
Lack of the proper laboratory report with proper recommendation	184	72.4
Absent awareness about the proper sampling timing and guidelines	173	68.1
Physicians are not informed about the available TDM tests	165	65.0
Lack of knowledge about TDM	115	45.3
Total	254	100

DISCUSSION

The current study was conducted through an electronic questionnaire based survey to study the level of awareness and attitude among the healthcare staff in Arar towards 'TDM' in terms of their genders, ages, years of experience, and specialties. Also the study aimed to highlight the main obstacles against proper use of TDM in Arar. The participants from the secondary health care service level were the majority of the physician enrolled in the study. Digitalis, theophylline, carbamazepine, vancomycin, and imipramine were the most commonly requested and known drugs for TDM among the participants. Regarding the awareness of the participants about the indication of TDM, suspected therapeutic failure and altered liver or kidney functions were the commonest indications known by the physicians enrolled in the study. Awareness about the drugs for TDM and the general indications of TDM was significantly higher among junior staff and physicians with less than 10 years' experience in the medical practice. Regarding the obstacles which limit application of TDM in Arar according to the participants' points of views, participants reported that lack of the proper laboratory reports with guiding recommendation was the most important point limiting their requesting for TDM. followed by lack of awareness about the proper timing of sampling and sampling guideline for TDM. Finally, postgraduate studies were the commonest source of knowledge about TDM.

More than 50% of the participants had reported requesting TDM during their practice in Arar. Carbamazepine, digitalis, theophylline and antibiotics were the main requested drugs for TDM. This is in accordance with Leung et al. (2019) who had reported the same drugs to e requested by the Canadian pediatrician[16]. It was noticed that these drugs are well known among physicians to be unsafe with narrow therapeutic index and this was the main motive to force them to follow these drugs serum levels. Also these drugs are mainly asked by certain specialties which are mined by their hazards. It was also of interest to know that the majority of persons who were keen to ask for TDM were junior physicians or physicians with lower than 10 years' medical experience.

Interestingly, Carbamazepine, digitalis, theophylline and antibiotics were also the most commonly reported by the participants as drugs for TDM. This shows expected relation between awareness and practice which was reported in other studies[17,18]. Regarding the knowledge of

the participants about the indications of TDM, therapeutic faire was the commonest, followed by cases with clinical or laboratory data for hepatic or renal affections with drugs with suspected hepatic of renal toxicity. The physicians were less interested to monitor the therapeutic levels in the beginning of therapy or with shifting from one drug to another. This is mainly due to the general believe among the physicians that they are treating the patient and not the drugs' serum levels. So their main interest is mainly focused on the patient symptoms and signs and the drugs' side effects and not mainly interested with the drugs serum levels. So therapeutic failure and drugs side effects are main triggers to request for TDM [19].

It was noticed that the awareness about the list of the drugs targeted by TDM assays and the indications for TDM id higher among the junior staff (registrar, residents, general practitioner and interns) in comparison with the senior staff (consultants and senior registrar). This mainly be due to most of senior staff are depending on their clinical experience to adjust doses and expect responses among their patients. In addition, junior staff as residents and registrar are already or recently graduated enrolled in postgraduate programs of training which more interested with the proper application of the available laboratory services for better patients' safety and better drug's efficacy with the least side effects[20].

Regarding the main obstacles against wide proper application for TDM lack of the proper laboratory reports with guiding recommendation was the most important point limiting their requesting for TDM. followed by lack of awareness about the proper timing of sampling and sampling guideline for TDM. Finally, postgraduate studies were the commonest source of knowledge about TDM.

The current data is important due to the following reasons. Results showed that awareness about TDM is fairly good but much more education and works shops activities should be considered for batter awareness between the physicians about TDM. Theses awareness should cover the importance of TDM data, drugs of interest, indications, sampling guidelines and the expected laboratory services. Also, some sort of obligation must be considered by including these TDM assays within the standard approved protocols for case management in the different specialties dealing with these medications targeted by TDM. It is also important to revised the considered obstacles by the participants, so proper revision of the laboratory report data is advised to encourage the physician to request more TDM specially with initiation of the medications. Also proper guideline about the timing of TDM sampling should be considered whether peak of random sampling and indications of each type and its drawbacks. These data for sampling can be written in the back of TDM request forms or circulated as a memo to help the physician for proper sampling. Finally, more interest for TDM should be considered in the undergraduate medical programs. This will be expected to improve the knowledge and attitude about TDM among the medical graduate.

CONCLUSION

Awareness about TDM among Doctors in Arar is fairly good. However, more work is required to improve the awareness among the physicians about TDM benefits, targeted drugs, indications to request TDM, and the proper sampling practices. This can be conducted through prepared series of scientific meeting and workshops about TDM. This is expected to maximize clinical benefit to TDM lab reports data for safe & effective drug prescriptions.

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