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SHORT COMMUNICATION

Sampling time and indications appropriateness for therapeutically monitored drugs at a teaching university hospital in Oman

Mohammed Al Za'abi [a,*], Juhina Al Muqbali [a], Khalid Al-Waili [b]

[a] *Department of Pharmacology & Clinical Pharmacy, College of Medicine & Health Sciences, Sultan Qaboos University, Oman*
[b] *Department of Biochemistry, College of Medicine & Health Sciences, Sultan Qaboos University, Oman*

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Abstract *Objective:* To evaluate prospectively the appropriateness of indications, sampling time and outcome of TDM requests at a teaching university hospital in Oman. *Methods:* A prospective cross-sectional study was conducted over a four months period; October 2013–January 2014 at the Sultan Qaboos University Hospital (SQUH), an 855 bed university teaching hospital. Appropriateness criteria for indications and sampling time were defined *a priori*. The evaluated drug's requests were for carbamazepine, phenytoin, phenobarbital, valproic acid, digoxin, gentamicin, amikacin, vancomycin, tobramycin, theophylline, lithium, and cyclosporine. *Results:* Of 733 evaluated TDM requisitions, the majority were for antibiotics (75.0%) followed by antiepileptics (10.5%) and cyclosporine (8.9%). Most of the requests had appropriate indication (78.2%), however, only 28.5% had appropriate sampling time. Results were applied by dosage adjustments in 65.8% of requests and some of the inappropriately sampled requests (15.3%) were used as a basis for modifying the dosage regimen. Of all the reported plasma concentrations 42.3%, 41.2%, and 16.5% were within, below and above the reference range, respectively. *Conclusion:* TDM service is much less than optimal in SQUH. A lot of effort needs to be carried out to improve TDM use in the developing countries as adjusting the doses on results that are based on wrong sampling time might expose patients to toxicity or therapeutic failure.

1. Introduction

Therapeutic drug monitoring (TDM) is an established useful clinical service in pharmacotherapy. It helps in identifying alternations in drug disposition, adjusting drugs' dosage regimen and minimizing adverse effects (Doogue and Martin, 2010; Eliasson et al., 2013; Mehler-Wex et al., 2009). It is widely applied to a variety of drug classes such as antibiotics,

* Corresponding author. Tel.: +968 2414 1155; fax: +968 2414 1107.
E-mail addresses: zaabi@squ.edu.om, alzaabimohd@gmail.com (M. Al Za'abi).
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Table 1 Patient's demographic and laboratory data.

		N (%)	Mean ± SD (range)/median (IQR)
Age (years)		733 (100)	25.38 ± 26.8 (0–85)
	Neonates	119 (16.2)	
	Infants	106 (14.5)	
	Children and Adolescence	150 (20.5)	
	Adults	358 (48.8)	
Gender	M	395 (53.9)	
	F	338 (46.1)	
Ordering units	Medical	370 (50.5)	
	Hematology	114 (30.8)	
	General	91 (24.6)	
	Others	109 (44.6)	
	Pediatric	236 (32.2)	
	Neonatal	98 (41.5)	
	Hematology	76 (32.2)	
	General	36 (15.3)	
	Others	26 (11.0)	
	Surgical	75 (10.2)	
	Pediatric	29 (38.7)	
	Cardio-thoracic	21(28.0)	
	General	18 (24.0)	
	Others	7 (9.3)	
	Others	52 (7.1)	
Weight (Kg)			39.92 ± 31.56 (0.67–150)

antiepileptics, immunosuppressant and others (Eliasson et al., 2013; Kang and Lee, 2009). Several studies found that inappropriate utilization of TDM such as inappropriateness in indications, sampling time and application of results, might lead to a significant waste of resources especially for developing countries (Norris et al., 2010; Ostad Haji et al., 2013; Nilsson et al., 2001; Ab Rahman et al., 2013; Ratanajamit et al., 2009; Dalaklioglu, 2013). In Oman, TDM use is limited for tertiary care hospitals, which are few. Among these is the Sultan Qaboos University Hospital (SQUH), a university teaching hospital, were TDM was introduced almost 15 years ago. In 2012 the total number of TDM requests was 6558. These were carried for the following drugs: carbamazepine, phenytoin, valproic acid, digoxin, phenobarbital, gentamicin, tobramycin, amikacin, vancomycin, theophylline, lithium, cyclosporine, and methotrexate. Two retrospective studies at SQUH one on antiepileptic drugs (AEDs) and the other on vancomycin, have been conducted. The evaluated AEDs TDM requests (354) showed that 50%, 37% and 13% of all reported concentrations were either below, within or above the therapeutic range, respectively (Al Za'abi et al., 2013a). Similarly the vancomycin study showed that 70.2% and 7.6% of the samples were either below or above the recommended range, respectively (Al Za'abi et al., 2013b). Despite the availability of this service there was no study documenting the appropriateness of sampling time and indications of these requests. Therefore the present study was performed to prospectively assess the appropriateness of indications, sampling time and outcome of TDM requests at SQUH.

2. Materials and methods

The study was a prospective, cross-sectional type. It was conducted over a four month period; October 2013 to January 2014 at SQUH, an 855 bed university teaching hospital. It included all TDM requests for inpatients. Patients were identified using TDM requests reaching the biochemistry laboratory where the measurements for drugs are usually carried out, and retrieved using the hospital information system program "Trackcare". A data collection sheet was created to collect the required information. It contained information regarding demographic data such as sex and age, request data such as unit, time, indications and results outcome. The drugs' concentrations were measured by an automated analyzer Roche \ Hitachi Cobas® systems.

Appropriateness criteria for indications and sampling time were defined *a priori* based on the literature and SQUH available TDM guidelines and the study was approved by the Sultan Qaboos University Medical Ethics Committee before commencing data collection.

Data are presented as frequencies and percentages and as mean and median where appropriate. Chi square test was used to explore the assassination between sex, age, nursing duties shifts, or ordering units and sampling time or indications appropriateness. A p values <0.05 were considered statistically significant.

3. Results

A total of 733 TDM requests during the four month collection period (October 2013–January 2014) that fulfilled the inclusions criteria were recruited and evaluated. Almost half of the requests (n = 395, 53.9%) were for males. Most of the patients were less than 18 years of age (n = 385, 52.5%) with a mean age and weight of 25.38 ± 26.8 years, 39.92 ± 31.56 kg, respectively.

Antibiotics were the most frequently (n = 550, 75%) monitored drugs in all age groups; 94.9%, 62.3, 65.0%, and 76.7%

Table 2 Indication and sampling time appropriateness.

Drug	*N* (%)	Dosage mean ± SD (range) mg	TDM results *N* (%)			Indication appropriateness *N* (%)		Sampling time appropriateness *N* (%)		
			Low	Within	High	Yes	No	Yes	No	Not clear
Carbamazepine	7 (1)	680 ± 540.37 (200–1600)	6 (85.7)	1 (14.3)	0	6 (85.71)	1 (14.28)	2 (28.57)	3 (42.85)	2 (28.57)
Valproic acid	12 (1.6)	1294.62 ± 1335.08 (57.64–4500)	10 (83.33)	2 (16.67)	0	11 (91.97)	1 (8.33)	3 (25)	9 (75)	0
Phenobarbital	27 (3.7)	55.42 ± 135.57 (3–600)	4 (14.8)	11 (40.74)	12 (44.44)	22 (81.48)	5 (18.5)	5 (18.5)	19 (70.37)	3 (11.11)
Phenytoin	31 (4.2)	159.8 ± 111.84 (12–400)	15 (48.39)	6 (19.35)	10 (32.26)	28 (90.32)	3 (9.67)	9 (29.03)	19 (61.3)	3 (9.67)
Lithium	10 (1.4)	860 ± 134.99 (800–1200)	4 (40)	6 (60)	0	9 (90)	1 (10)	7 (70)	2 (20)	1 (10)
Theophylline	2 (0.3)	300 ± 0 (300–300)	1 (50)	1 (50)	0	0	2 (100)	0	2 (100)	0
Digoxin	29 (4)	135.78 ± 71 (62.5–250)	12 (41.4)	15 (51.72)	2 (6.89)	23 (79.31)	6 (20.68)	2 (6.89)	26 (89.65)	1 (3.44)
Cyclosporine	65 (8.9)	179 ± 100.9 (25–400)	15 (23)	41 (63)	9 (14)	51 (78.46)	14 (21.53)	25 (38.46)	38 (58.46)	2 (3.07)
Amikacin	84 (11.5)	240.8 ± 339.08 (9–1500)	56 (66.67)	11 (13.09)	17 (20.23)	52 (61.9)	32 (38)	16 (19)	65 (77.3)	3 (3.57)
Gentamicin	218 (29.8)	173.87 ± 173.1 (2.5–560)	107 (49.08)	105 (48.16)	6 (2.75)	161 (73.85)	57 (26.14)	94 (40.82)	124 (59.17)	0
Vancomycin	248 (33.8)	1399.44 ± 885.2 (21.2–6000)	72 (29)	111 (44.76)	65 (26.2)	210 (84.68)	38 (15.32)	46 (18.54)	161 (64.9)	41 (16.53)
Tobramycin	0	–	–	–	–	–	–	–	–	–
Total	733 (100)	–	302 (41.2)	310 (42.3)	121 (16.5)	573 (78.17)	160 (21.8)	209 (28.5)	468 (63.8)	56 (7.64)

in neonates, infants, children and adults, respectively followed by AEDs (n = 77, 10.5%) and cyclosporine (n = 65, 8.9%). The majority of the requests were ordered by medical units (n = 370, 50.5%) followed by pediatric units (n = 236, 32.2%) and surgical units (n = 75, 10.2%). Table 1 illustrates the patient's demographic and laboratory data while Table 2 illustrates the monitored drugs.

TDM plasma concentration results were compared with the reference range of each drug and classified into low, within, and high. Among all the requests, 310 (42.3%) were within the range, 302 (41.0%) were lower than the range, and 121 (16.5%) were higher than the range.

Most of the requests had appropriate indications (n = 573, 78.2%). Majority of these were indicated as initial monitoring for the dosage regimen (n = 347, 60.5%) followed by a change in dosage (n = 84, 14.7%). Most of the inappropriate indications (n = 82, 51.3%) were for pre levels of a once daily dosing regimen of amikacin and/or gentamicin followed by orders where TDM is not needed (n = 50, 31.3%). Inappropriate indications were higher among patients <18 years than patients >18 years (23.9% *v.* 17.8%; p = 0.048). Furthermore, inappropriate indications was statistically higher in pediatric units (28.0%) than medical (18.7%) or surgical (9.3%) ones (p = 0.001) (Table 3).

Sampling time was found to be appropriate in only 28.5% (n = 209) of requests. Most of inappropriateness (n = 468, 63.8%) was due to wrong sampling time (n = 409, 55.8%) or did not reach the study state concentrations (n = 59, 8%). In 7.6% (n = 56) of requests the sampling times were not clear. Inappropriateness was more in patients <18 years of age (73.6% *v.* 64.2%; p = 0.008) and with more requests from surgical units than pediatrics or medical units (82.2%, 75.7% and 59.9%; respectively, p = 0.001). There was no significant statistical association between the sampling time appropriateness and sex or different nursing duty shifts.

The results of TDM requests were mostly applied (n = 482, 65.8%) by adjusting the dosage regimen as required. Among these, 50.0% (n = 280) required no change, in 16.1% (n = 77) doses were increased and in 9.8% (n = 47) doses were reduced or stopped/withhold. Only a quarter (n = 178, 24.3%) had inappropriate application where a required change did not occur. In 50 and 62 of requests (15.3%) the dosage regimens were increased and reduced, respectively, based on inappropriate sampling time results.

4. Discussion

TDM is an important service that helps in improving dose individualization, assessing compliance and reducing toxicity. Thus there is an increase in demand for this service which lead to an increase in hospital cost and gauges for more resources (Eliasson et al., 2013; Westin et al., 2012). For the developing countries where there is a paucity of resources, appropriate utilization of TDM is of paramount importance with other services. The result of this audit showed that there is considerable work is needed to be done in order to improve this service in our setting. Among these is the substantial percentage (71.5%) of inappropriate sampling time. These results are somehow comparable to the rest of the developing countries. Due to the nature of drugs undergoing TDM, it is imperative to emphasis the importance of sampling time as correct

Table 3 Association of indications and sampling time appropriateness with patients' characteristics, nursing duty shifts, and ordering units.

Variable	Sampling time appropriateness			Indication appropriateness		
	Appropriate *n* (%)	Inappropriate *n* (%)	*p*	Appropriate *n* (%)	Inappropriate *n* (%)	*p*
Gender						
• Male	104 (28.8)	257 (71.2)	0.237	317 (80.3)	78 (19.7)	0.417
• Female	104 (33.0)	211 (67.0)		263 (77.8)	75 (22.2)	
Age (years)						
• < 18	95 (26.4)	265 (73.6)	0.008	284 (76.1)	89 (23.9)	0.048
• > = 18	113 (35.8)	203 (64.2)		296 (82.2)	64 (17.8)	
Nursing duty shifts (time)						
• 07:30–14:00	63 (29.9)	148 (70.1)	0.117	–	–	–
• 14:00–21:30	67 (36.6)	116 (63.4)		–	–	
• 21:30–7:30	78 (27.7)	204 (72.3)		–	–	
Ordering units						
• Medical	115 (40.1)	172 (59.9)	0.000	266 (81.3)	61 (18.7)	0.001
• Pediatrics	65 (24.3)	203 (75.7)		201 (72.0)	78 (28.0)	
• Surgical	13 (17.8)	60 (82.2)		68 (90.7)	7 (9.3)	
• Others	15 (31.3)	33 (68.8)		45 (86.5)	7 (13.5)	

interpretation of TDM results very much depends on the information on sampling time and duration of therapy. Adjusting the doses on results that are based on wrong sampling time might expose patients to toxicity or therapeutic failure. Digoxin, for example, in this study and other studies in the developed countries was sampled before it reaches the steady state (Sidwell et al., 2003; Mordasini et al., 2002). This might lead to unnecessary higher or lower than appropriate therapeutic dosage regimen.

The aminoglycoside antibiotics gentamicin and amikacin and vancomycin were the major drugs (75.0%) to be monitored in this study perhaps due to the inclusion of inpatients only. Therefore, these antibiotics represent most of the TDM cost. It was also found that most of the inappropriate sampling time (51.3%) was for these antibiotics. The results of these samples were considered in the dosage regimen in some patients. This might increase the chance for emergences of resistant infections which in turn might affect treated patients and may be the community at large.

Plasma concentration results in our study showed that 310 of requests (42.3%) were within the therapeutic ranges requiring no change in the dosage regimen. Another 302 requests (41.2%) had low plasma concentrations that might require an increase in the dosage regimen and therefore the dose was increased in 73 (24.2%) of them. There were 121 requests (16.5%) with high plasma concentrations where reducing, stopping, or withholding of the dosage regimen occurred in 93 (76.9%) of them. This shows that dosage regimens were changed more frequently with toxic plasma concentrations than with sub therapeutic concentrations. It seems that physicians are more concerned about toxic results than sub-therapeutic concentrations. Although this sometimes might be related the patients' clinical status, however, sub-therapeutic concentrations may lead to the failure of therapy and development of resistance to some drugs like antibiotics and might also lead to increased length of hospitalization and health care costs. This trend has also been observed elsewhere (Ratanajamit et al., 2009; Dalaklioglu, 2013; Taur et al., 2013). Sub-therapeutic concentrations should be as clinically alarming as toxic concentrations as failure of therapy and appearance of toxicity should be considered equally.

There was no significant statistical association between the sampling time appropriateness and different nurses' duty shifts. This might suggest that different working time has no effect on sampling time appropriateness but rather, it might be the lack of knowledge about sampling time. Statistically it was also shown that more inappropriate sampling times occurred among patients younger than 18 years and more among orders requested from surgical units. There are no clear reasons why this might be the case.

As with all studies we could identify some limitations. For example, the assessment of indications was retrieved from TDM requests for which we cannot assure that the supplied information was complete or correct. It also should be taken into account that the dose adjustments should never be made on the basis of serum drug concentrations alone but should be justified after careful assessment of the patient's clinical status. Finally, the impact of changing the dosage regimen based on the interpretation of results with inappropriate sampling time on the patient and health care system could not be measured.

5. Conclusion

This audit identified several issues that need to be undertaken in order to optimize TDM in our setting. It also raises several points such as the need of increasing the involvement of pharmacists in TDM service as their presence during clinical rounds has been shown to reduce inappropriateness and monitoring costs (Ratanajamit et al., 2009). It also raises the query to policy makers to decide whether it is more economically favorable to consolidate resources in the pharmacy department and biochemistry department than current practice.

Declaration of interest

None.

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