SHORT COMMUNICATION

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

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Received 12 August 2014; accepted 17 November 2014
Available online 24 November 2014

Keywords
Therapeutic drug monitoring; Developing countries; Plasma concentrations

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.

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1. Introduction

Therapeutic drug monitoring (TDM) is an established useful clinical service in pharmacotherapy. It helps in identifying alterations 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,
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 

| Table 1 Patient’s demographic and laboratory data. |
|-----------------------------------------------|
| **N (%)** | **Mean ± SD (range)/median (IQR)** |
| Age (years) | |
| Neonates | 119 (16.2) | 25.38 ± 26.8 (0-85) |
| 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) |

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%
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 \((n = 84, 14.7\%)\). Inappropriate indications were higher among patients <18 years \((23.9\%\ vs. 17.8\%; \(p = 0.048\)) and surgical units \((28.2\%)\ vs. medical \((18.7\%)\ vs. surgical \((9.3\%)\; \(p = 0.001\)) (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. Inappropriate indications was more in patients <18 years \((73.6\%\ vs. 64.2\%; \(p = 0.008\)) with more requests from surgical units than pediatrics or medical units \((82.2\%, 75.7\%\ and 59.9\%; \(p = 0.001\)) (Table 3). 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 emphasize the importance of sampling time as correct
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 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 biochemistry department than current practice.

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; Dalakioglou, 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.
References

Ab Rahman, A.F., Ahmed Abdelrahim, H.E., Mohamed Ibrahim, M.I., 2013. A survey of therapeutic drug monitoring services in Malaysia. Saudi Pharm. J. 21, 19–24.

Al Za’abi, M., Ahmed, R., Al Asmi, A., Al-Zakwani, I., 2013a. Utilization patterns of antiepileptic drugs among adult epileptic patients at a tertiary hospital in Oman. Int. J. Pharm. Pract. 21, 117–122.

Al Za’abi, M., Shafiq, S., Al Riyami, D., Ali, B.H., 2013b. Utilization pattern of vancomycin in a university teaching hospital in Oman: comparison with international guidelines. Trop. J. Pharm. Res. 12, 117–121.

Dalaklioglu, S., 2013. Evaluating appropriateness of digoxin, carbamazepine, valproic acid, and phenytoin usage by therapeutic drug monitoring. Clin. Lab. 59, 325–331.

Doogue, M.P., Martin, J.H., 2010. Whither therapeutic drug monitoring? Intern. Med. J. 40, 671–672.

Eliasson, E., Lindh, J.D., Malmstrom, R.E., Beck, O., Dahl, M.L., 2013. Therapeutic drug monitoring for tomorrow. Eur. J. Clin. Pharmacol. 69 (Suppl. 1), 25–32.

Kang, J.S., Lee, M.H., 2009. Overview of therapeutic drug monitoring. Korean J. Intern. Med. 24, 1–10.

Mehler-Wex, C., Kolch, M., Kirchheiner, J., Antony, G., Fegert, J.M., Gerlach, M., 2009. Drug monitoring in child and adolescent psychiatry for improved efficacy and safety of psychopharmacotherapy. Child Adolesc. Psychiatry Ment. Health 3, 14.

Mordasini, M.R., Krahenbuhl, S., Schlienger, R.G., 2002. Appropriateness of digoxin level monitoring. Swiss Med. Wkly. 132, 506–512.

Nilsson, L., Bergman, U., Diwan, V., Farahmand, B.Y., Persson, P.G., Tomson, T., 2001. Antiepileptic drug therapy and its management in sudden unexpected death in epilepsy: a case-control study. Epilepsia 42, 667–673.

Norris, R.L., Martin, J.H., Thompson, E., Ray, J.E., Fullinfaw, R.O., Joyce, D., Barras, M., Jones, G.R., Morris, R.G., 2010. Current status of therapeutic drug monitoring in Australia and New Zealand: a need for improved assay evaluation, best practice guidelines, and professional development. Ther. Drug. Monit. 32, 615–623.

Ostad Haji, E., Mann, K., Dragicevic, A., Muller, M.J., Boland, K., Rao, M.L., Fric, M., Laux, G., Hiemke, C., 2013. Potential cost-effectiveness of therapeutic drug monitoring for depressed patients treated with citalopram. Ther. Drug. Monit. 35, 396–401.

Ratanajamit, C., Kaewpibal, P., Setthawacharavanich, S., Farooq, S., 2009. Effect of pharmacist participation in the health care team on therapeutic drug monitoring utilization for antiepileptic drugs. J. Med. Assoc. Thai. 92, 1500–1507.

Sidwell, A., Barclay, M., Begg, E., Moore, G., 2003. Digoxin therapeutic drug monitoring: an audit and review. N. Z. Med. J. 116, U708.

Taur, S.R., Kulkarni, N.B., Gogtay, N.J., Thatte, U.M., 2013. An audit of therapeutic drug monitoring services of anticonvulsants at a tertiary care hospital in India. Ther. Drug. Monit. 35, 183–187.

Westin, A.A., Larsen, R.A., Espnes, K.A., Spigset, O., 2012. Therapeutic drug monitoring (TDM) repertoire in Norway. Tidsskr. Nor. Laegeforen. 132, 2382–2387.