Full Length Research Paper

Therapeutic antiepileptic drug monitoring pattern in a tertiary care hospital in Oman

Mohammed Al Za'abi[1]*, Abdullah Al Asmi[2], Rowayda Ahmed[1], Safiya Al-Masrouri[3], Rihab Al-Lawati[3], Ramachandiran Nandhagopal[2] and Ibrahim Al-Zakwani[1]

[1]Department of Pharmacology and Clinical Pharmacy, Sultan Qaboos University Al Khoud, P. O. Box 35, Postal code 123, Sultanate of Oman.
[2]Department of Medicine, Sultan Qaboos University Al Khoud, P. O. Box 35, Postal code 123, Sultanate of Oman.
[3]College of Medicine and Health Sciences, Sultan Qaboos University Al Khoud, P. O. Box 35, Postal code 123, Sultanate of Oman.

In epilepsy, therapeutic drug monitoring (TDM) could aid in individualizing dosage regimen and ascertaining compliance on anti-epileptic drugs (AEDs). The aim of this study was to survey the requests for TDM of AEDs to determine drugs involved, observed concentrations, reasons for requests and action undertaken. TDM requests for AEDs were surveyed at a university hospital in Oman from January 2006 to December 2009. A total of 151 patients with 354 TDM requests were collected. These requests were for valproic acid (46.9%), phenytoin (26.8%), carbamazepine (25.4%) and phenobarbital (0.8%). 50, 37 and 13% of all reported concentrations were below, within and above therapeutic range, respectively. For majority of the subjects (70%), there were no clear reasons for plasma concentrations to lie outside the therapeutic range. No change in the drug therapy/dosing was required subsequent to the TDM reports in 42.7% of the cases. Emergency department was the main unit requesting TDM (63.8%) and TDM was mostly indicated for an increase in the seizures frequency on the same day (62.7%). This study provides an overview of the specific requests for TDM of AEDs in routine clinical practice which might help in auditing and improving this service for optimal utilization.

Key words: Antiepileptic drugs, therapeutic drug monitoring, epilepsy, plasma.

INTRODUCTION

Therapeutic drug monitoring (TDM) is a useful tool in individualizing drug therapy, enhancing drug's efficacy and improving patient's safety (Kang and Lee, 2009). Epilepsy is one of the most common disorders in which TDM has been utilized for optimizing pharmacotherapy (Eadie, 1976; Kutt and Penry, 1974). This is due to the pharmacokinetic characteristics of the most commonly used drugs such as carbamazepine, phenytoin, phenolbarbital and valproic acid in the developing countries. These antiepileptic drugs (AEDs) have narrow therapeutic indices, inter-individual pharmacokinetic variations, multiple drug interactions, pharmacokinetic interactions and a good correlation between plasma concentrations and clinical efficacy and safety (Johannessen and Tomson, 2006; Patsalos and Perucca, 2003, Patsalos et al., 2008; Toledano and Gil-Nagel, 2008). TDM could also help in ascertaining patient's compliance with AED. In contrary to older AEDs, the newer AEDs such as levetiracetam, topiramate and tigabine have less drug interaction profile, larger therapeutic indices and more predictable pharmacokine- tic profiles (Hachad et al., 2002; Zaccara et al., 2006). Moreover, there is no clear correlation between TDM and clinical efficacy or adverse effects of the newer AEDs. Thus, TDM has little, if any, clinical role in the manage- ment of epileptic patients on newer AEDs (Krasowski, 2010; Neels et al., 2004; Striano et al., 2008).

---
*Corresponding author. Email: zaabi@squ.edu.om. Tel: +96824141155. Fax: +96824141107.

At Sultan Qaboos University Hospital (SQUH), a university teaching hospital in Oman, monitoring of the free plasma concentrations is available for carbamazepine, valproic acid and phenytoin and total serum concentrations for phenobarbital. The aim of this survey of requests for TDM is to identify the drugs involved, the plasma concentrations observed, the reasons for the requests and clinical actions taken towards the results.

METHODOLOGY

This study was part of a utilization study of AEDs in adult (>18 years) epileptic patients undertaken over a period of 4 years from January 2006 to December 2009 at SQUH. All the TDM requests for AEDs were collected retrospectively from the electronic patients' records where the requests were punched in. Plasma concentrations were measured by fluorescence polarization immunoassay using semiautomatic analyzer (Roche Diagnostic Systems, USA). A standard TDM data sheet included information on epilepsy type and cause(s), co-morbidities, list of prescribed AEDs, frequency of seizures and the indications for TDM, apart from demographic characteristics.

This study was approved by the SQU Medical Research and Ethics Committee. For categorical variables, frequencies and percentages were reported. For continuous variables, means and standard deviation were used to summarize the data. Statistical analyses were performed using Statistical Package of Social Sciences version 15 (SPSS. Inc., Chicago, IL, USA).

RESULTS

A total of 151 patients with 354 TDM requests were collected (2.32 requests per patient) over the 4-year study period. The mean age of the patients was 34.6 ± 14.3 years (range 19 to 93 years) with a male to female ratio of 1.3:1.

Drugs that were prescribed along with the monitored AEDs were levetiracetam (19.8%), clonazepam (15.3%), topiramate (14.4%) and lamotrigine (12.4%). Majority of the patients (62.7%) have had a seizure on the same day of the TDM request. However, information about the pattern, type or frequency of seizures could not be determined reliably in some of the cases (22.3%). Emergency department was the main unit for requesting TDMs (63.8%) and these were mostly indicated for an increase in seizures frequency (69.8%) and suspected side effects (7.9%).

Table 1 summarizes the frequency of seizures, TDM indications, the locations for ordering TDM requests and possible reasons for sub-therapeutic and above therapeutic concentrations, while Table 2 lists the clinical actions taken towards the concentrations outlying the therapeutic range for the monitored AEDs. Majority of the TDM requests were for valproic acid (46.9%) followed by phenytoin (26.8%), carbamazepine (25.4%) and phenolbarbital (0.8%).

The reported concentrations that were lying below the therapeutic range, within the therapeutic range and above the therapeutic range were 50, 37 and 13%, respectively. No clear clinical reasons were identified in majority of the cases (70%) in whom the plasma concentration was outside the therapeutic ranges. Furthermore, there were no clinical actions taken towards these concentrations in many of these cases (42.7%). Poor compliance with the treatment regimen was difficult to be evaluated and it was only apparent in 24.2% of the requests.

DISCUSSION

In this study, 354 TDM requests for 151 patients were surveyed retrospectively at a university hospital in Oman. The most requested plasma concentrations were for valproic acid (46.9%) followed by phenytoin (26.8%), carbamazepine (25.4%) and phenobarbital (0.8%). Majority of these requests were ordered from the emergency department (63.8%) for patients presenting with seizures on the same day of the request. Half of all the requests (50%) were below the therapeutic range, while the other was either within (37%) or above (13%) the therapeutic range. A seizure due to poor compliance to medication was apparent in only 24.2% of the requests.

Despite decades of use of TDM of AEDs in the management of epilepsy, the correlation between the TDM and clinical efficacy of AEDs is not fully clear (Camfield and Camfield, 2006; Chan and Beran, 2008; Dreyfus, 2010; Glauser and Pippenger, 2000; Jannuzzi et al., 2000; Johannessen and Landmark, 2008). TDM have been used with almost all old AEDs, but such use has declined with time. This is partly due to the introduction of newer AEDs (Schmidt, 2009). In developing countries, TDM of older AEDs is requested in the setting of suspected problems with drug compliance, adverse effects or overdose (Jose et al., 2006; Palmini, 2000; Radhakrishnan, 2009). The same indications were observed in this study. Thus, the main indication for TDM requests was an increase in seizure frequency (69.8%) possibly due to suspected insufficient plasma concentrations of AEDs. Most of these seizure occurred at the same day of the requests (62.7%). Poor compliance was apparent in only 24.2% of the subjects. However, it might be attributed to the reported sub-therapeutic concentrations in most of the subjects (50%), though it could not be ascertained. This could also be supported from the finding that no actions were taken towards the sub-therapeutic reported concentrations in most of the subjects (42.7%). Furthermore, for the three drugs: carbamazepine, phenytoin and valproic acid, most of the subjects were discharged with the same dosage regimen they were on before experiencing seizures. This might indicate that TDM played little, if any, role in the clinical management of the patients. Similar conclusions have been reached in previous studies (Jannuzzi et al.,

Table 1. Frequency of seizures, TDM indications, the locations of TDM requests and reasons for sub-therapeutic and above therapeutic range concentrations.

Parameter	N (%)
Frequency of seizures/month	
<3	29 (8.2)
4-6	19 (5.4)
>6	20 (5.6)
Information not available	247 (69.8)
Others	39 (11.0)
Time of last episode of seizure(s) to TDM request	
Same day	222 (62.7)
Same week	35 (9.9)
Within 4 weeks	10 (2.8)
1-3 months	3 (0.8)
> 3 months	5 (1.4)
Information not available	79 (22.3)
Indications for TDM request	
Side effects	28 (7.9)
Increase seizures frequency	247 (69.8)
Routine	22 (6.2)
Upward titration of dose	21 (5.9)
Others	36 (10.2)
Locations of the TDM request	
Emergency department	226 (63.8)
Outpatient department	
Neurology	15 (4.2)
Psychiatry	15 (4.2)
Others	5 (1.4)
Inpatients wards Medical	62 (17.5)
Psychiatric	7 (2.0)
ICU	11 (3.1)
Others	13 (3.7)
Reasons for therapeutic range outliers (n = 223)	
Toxic concentrations (n = 46)	
Errors in taking the drugs	3 (6.5)
Interaction with other drugs	1 (2.2)
Unclear reasons	42 (9.3)
Subtherapeutic concentrations (n = 177)	
Poor compliance	54 (30.5)
Out of medication	8 (4.5)
Interaction with other drugs	1 (0.6)
Unclear reasons	114 (64.4)

2000; Minshall et al., 2011; Sharma et al., 2009; Walters et al., 2004). Other subjects required the addition of another drug (15.0%), an increase or a decrease in the dosage regimen (17.5%) or completely stopping the drug (5.1%). This might be an indication to ineffectiveness of the drug, insufficient plasma concentrations or intolerable

Table 2. Clinical actions taken towards the concentrations outlying the therapeutic range for valproic acid, carbamazepine and phenytoin.

Parameter	Valproic acid n = 166 (%)	Carbamazepine n = 90 (%)	Phenytoin n = 95 (%)
None	73 (44.0)	47 (52.2)	31 (32.6)
Increased the current dose	29 (17.5)	7 (7.8)	12 (12.6)
Decreased the current dose	3 (1.8)	6 (6.7)	5 (5.3)
Stopped the drug	3 (1.8)	5 (5.6)	10 (10.5)
Added another drug	27 (16.3)	11 (12.2)	18 (18.9)
Restarted the same drug	26 (15.7)	9 (10.0)	17 (17.9)
Other	5 (3.0)	5 (5.6)	2 (2.1)

side effects. In general, due to significant fluctuations in the plasma concentrations of sodium valproate, determination of valproate level is being discouraged (Shorvon, 2010). Since the timing of the blood collection with regard to the last dose of AEDs was not available, it was difficult to determine whether the plasma level reflected trough or peak concentration.

The concept of "therapeutic range" for AEDs has always been debated (Jannuzzi et al., 2000; Johannessen and Landmark, 2008; Patsalos et al., 2008; Tomson et al., 2007). While some patients might be well controlled with plasma concentrations well below the therapeutic range, others might require a higher than therapeutic range plasma concentrations without demonstrating unacceptable adverse effects. To overcome the limitations that aroused with the "therapeutic range", the concept "individual therapeutic concentration" emerged and appeared to be well accepted (Jannuzzi et al., 2000; Johannessen and Landmark, 2008; Patsalos et al., 2008; Tomson et al., 2007). Thus, TDM of AEDs has become more rewarding in selected patients with specific clinical conditions and for specific AEDs. Furthermore, pharmacogenomics also play a role in the inter-individual differences in AEDs concentrations (Cavalleri et al., 2011; Pandolfo, 2011). A prospective study incorporating pharmacogenomics would aid in individualizing therapy in certain patients in this era of personalized medicine.

Owing to the nature of the clinical presentations of seizures, majority of these requests were ordered from the emergency department. Epilepsy at SQUH is primarily managed by neurology unit, despite the fact that only 4.2% of all requests originated from this unit. This might reflect an awareness and adherence to the current guidelines in adopting selective request for TDM of AEDs (Minshall et al., 2011; Patsalos et al., 2008).

Several questions emerged while interpreting the collected data and could not be well resolved. Potential concerns were: was the reported concentration trough or peak? Was the sampling time appropriate for these concentrations? Was the reported values steady state concentrations? What was the nature of drug interactions?

Conclusion

This study provides an overview of the specific requests for TDM of AEDs in routine clinical practice and this could be the first step towards subsequent auditing of this laboratory service for optimal utilization. The results of this study suggest that the TDM of older AEDs can still be of some value in the management of patients with epilepsy mainly if indicated for therapeutic noncompliance, exploring sub-therapeutic concentrations and toxicity which might aid in subsequent clinical decision.

REFERENCES

Camfield P, Camfield C (2006). Monitoring for adverse effects of antiepileptic drugs. Epilepsia 47 Suppl 1(31-34).

Cavalleri G, Mccormack M, Alhusaini S, Chaila E, Delanty N (2011). Pharmacogenomics and epilepsy: the road ahead. Pharmacogenomics 12(10):1429-1447.

Chan K, Beran R (2008). Value of therapeutic drug level monitoring and unbound (free) levels. Seizure 17(6):572-575.

Dreyfus D (2010). The usefulness of measuring antiepileptic medication blood levels in patients with epilepsy. Am. Fam. Physician 82(9):1070.

Eadie M (1976). Plasma level monitoring of anticonvulsants. Clin. Pharmacokinet. 1(1):52-66.

Glauser T, Pippenger C (2000). Controversies in blood-level monitoring: reexamining its role in the treatment of epilepsy. Epilepsia 41 Suppl 8(S6-15).

Hachad H, Ragueneau-Majlessi I, Levy R (2002). New antiepileptic drugs: review on drug interactions. Ther. Drug Monit. 24(1):91-103.

Jannuzzi G, Cian P, Fattore C, Gatti G, Bartoli A, Monaco F, Perucca E (2000). A multicenter randomized controlled trial on the clinical impact of therapeutic drug monitoring in patients with newly diagnosed epilepsy. The Italian TDM Study Group in Epilepsy. Epilepsia 41(2):222-230.

Johannessen S, Landmark C (2008). Value of therapeutic drug monitoring in epilepsy. Expert Rev. Neurother. 8(6):929-939.

Johannessen S, Tomson T (2006). Pharmacokinetic variability of newer antiepileptic drugs: when is monitoring needed? Clin. Pharmacokinet. 45(11):1061-1075.

Jose V, Medhi B, Pandhi P (2006). Antiepileptic TDM pattern at a tertiary care hospital in India. Nepal Med. Coll. J. 8(2):107-110.

Kang J, Lee M (2009). Overview of therapeutic drug monitoring. Korean J. Int. Med. 24(1):1-10.

Krasowski M (2010). Therapeutic Drug Monitoring of the Newer Anti-Epilepsy Medications. Pharmaceuticals (Basel) 3(6):1909-1935.

Kutt H and Penry J (1974). Usefulness of blood levels of antiepileptic drugs. Arch. Neurol. 31(5):283-8.

Minshall I, Berry D, Smith D (2011). The impact of an educational intervention, the New GP Contract and NICE guidelines on anti-epilepsy therapeutic drug monitoring. Seizure 20(2):126-130.

Neels H, Sierens A, Naelaerts K, Scharpe S, Hatfield G, Lambert W (2004). Therapeutic drug monitoring of old and newer anti-epileptic drugs. Clin. Chem. Lab. Med. 42(11):1228-1255.

Palmini A (2000). Medical and surgical strategies for epilepsy care in developing countries. Epilepsia 41 Suppl 4(S10-17).

Pandolfo M (2011). Genetics of epilepsy. Semin. Neurol. 31(5):506-18.

Patsalos P, Berry D, Bourgeois B, Cloyd J, Glauser T, Johannessen S, Leppik I, Tomson T, Perucca E (2008). Antiepileptic drugs-best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia 49(7):1239-1276.

Patsalos P, Perucca E (2003). Clinically important drug interactions in epilepsy: general features and interactions between antiepileptic drugs. Lancet Neurol. 2(6):347-356.

Radhakrishnan K (2009). Challenges in the management of epilepsy in resource-poor countries. Nat. Rev. Neurol. 5(6):323-330.

Schmidt D (2009). Drug treatment of epilepsy: options and limitations. Epilepsy Behav. 15(1):56-65.

Sharma S, Joshi S, Mukherji S, Bala K, Tripathi C (2009). Therapeutic drug monitoring: appropriateness and clinical utility in neuropsychiatry practice. Am. J. Ther. 16(1):11-16.

Shorvon S (2010) Handbook of Epilepsy Treatment, Wiley-Blackwell.

Striano S, Striano P, Capone D, Pisani F (2008). Limited place for plasma monitoring of new antiepileptic drugs in clinical practice. Med. Sci. Monit. 14(10):RA173-178.

Toledano R, Gil-Nagel A (2008). Adverse effects of antiepileptic drugs. Semin. Neurol. 28(3):317-27.

Tomson T, Dahl M, Kimland E (2007). Therapeutic monitoring of antiepileptic drugs for epilepsy. Cochrane Database Syst. Rev. (1):CD002216.

Walters R, Hutchings A, Smith D, Smith P (2004). Inappropriate requests for serum anti-epileptic drug levels in hospital practice. QJM: Int.J. Med. 97(6):337-341.

Zaccara G, Messori A, Cincotta M, Burchini G (2006). Comparison of the efficacy and tolerability of new antiepileptic drugs: what can we learn from long-term studies? Acta. Neurol. Scand. 114(3):157-168.