

Accepted author version posted online: 15 September 2016

**PHARMACIST-MANAGED THERAPEUTIC DRUG MONITORING SERVICE OF ANTIEPILEPTIC
DRUGS IMPROVED SEIZURE CONTROL**

CHUN WAI CHANG* AND SIVARAJ RAMAN

Hospital Keningau, Peti Surat 11, 89007 Keningau, Sabah, Malaysia

*Corresponding author: leckaschang@gmail.com

Running head: Therapeutic Drug Monitoring and Seizure Control

Although therapeutic drug monitoring (TDM) has been used in practice, there are conflicting data on its usefulness in the management of epilepsy. These range from having no significant differences in patients' clinical outcomes to being a cost-effective service. Thus, this study was conducted to evaluate the effectiveness of our pharmacist-managed TDM service in helping patients with epilepsy (PWE) to achieve seizure control. This was a retrospective observational study conducted in TDM Unit of Hospital Keningau, Sabah. Pharmacists-prepared reports of 30 subjects with uncontrolled seizure in 2014 were analysed for the effectiveness of their recommendations. The effectiveness was measured based on number of patients that achieved $\geq 50\%$ reduction in seizure frequency and the number of patients with 3-month seizure free period. 80% of pharmacists' TDM recommendations were accepted by prescribers. Based on the data collected, 17 (56.67%) subjects had their seizure frequency decreased at least by half while 11 (36.67%) subjects achieved total remission. However, there was no significant association between the accepted recommendations and the seizure control. A non-statistically significant 1.4 times higher odds that pharmacist's recommendation was able to help PWE to achieve seizure control was found. In conclusion, pharmacist-managed TDM service is able to improve the seizure control in more than 50% of PWE with unsatisfactory seizure control.

Keywords: Therapeutic drug monitoring (TDM), Pharmacist, Effectiveness

INTRODUCTION

Therapeutic drug monitoring (TDM) is the measurement of the concentration of a prescribed xenobiotic or endogenous compound made in the laboratory that, with appropriate interpretation, will directly influence prescribing procedures (Watson et al. 1997). TDM has been employed in the management of epilepsy since its introduction more than 40 years ago (Taur et al. 2013).

In Malaysia, TDM service is available since 1984 (Rahman, Abdelrahim and Ibrahim 2013). The first facility to offer this service was Hospital Universiti Sains Malaysia. In 2006, there were 78 government hospitals in Malaysia offering TDM service (Rahman, Abdelrahim and Ibrahim 2013). Official record

showed that there were a total of 61907 cases monitored by TDM in year 2005 alone in Malaysia (Rahman, Abdelrahim and Ibrahim 2013). In the hospitals with TDM service, this service is handled by the pharmacists.

Although TDM has been used in practice for decades, there were conflicting data on its usefulness in the management of epilepsy. A multicentre randomized controlled trial by Januzzi et al. (2000) found no significant difference in the clinical outcome of patients with newly diagnosed epilepsy. However, there were two pharmacoeconomic studies in India (Rane et al. 2001) and Malaysia (Salih et al. 2013) that demonstrated TDM is cost-effective in patients with adult onset epilepsy and in specific paediatric population respectively. The authors of a review which found no clear evidence for the use of TDM in patients with newly-diagnosed epilepsy nonetheless suggested that TDM may be useful for polytherapy, in special situations or in selected patients (Tomson, Dahl and Kimland 2007).

In our hospital, TDM service is provided by the pharmacy department. The prescriber will identify the patients with epilepsy (PWE) who require the service and refer them to the pharmacists. The frequency of seizure attack, compliance and experience of side effects will be elicited from the patients. If the patient is admitted to the ward, the pharmacist will also monitor the progress of patient in the ward. The results will be interpreted by pharmacists and a report with recommendation for each patient will be given to the ordering prescriber. The prescriber will decide to accept or reject the recommendation based on clinical judgement. The antiepileptic drugs (AEDs) that we monitor include carbamazepine, phenobarbitone, phenytoin and valproic acid.

As the effect of TDM on the clinical outcome of PWE is not clear, we conducted this study to evaluate the effectiveness of our pharmacist-managed TDM service in helping PWE to achieve seizure control.

METHODS

Study Design

This was a retrospective observational study conducted in TDM Unit, Hospital Keningau, Sabah, Malaysia. PWE were referred for TDM service when the prescriber deemed it was necessary. The results were interpreted by pharmacists and a report with recommendation was given to the ordering prescriber. It was up to the clinical judgement of the prescriber to accept or reject the recommendation. The AEDs which were monitored include carbamazepine (reference range: 4 – 12 mg/L), phenobarbitone (15 – 40 mg/L), phenytoin (10 – 20 mg/L) and valproic acid (50 – 100 mg/L).

Data was obtained from the TDM reports for year 2014. Types of data that we collected include age, gender, type of AEDs, dates of sampling, seizure frequency, measured plasma levels of antiepileptic drugs and the status of recommendation (accepted or rejected by the requesting prescriber).

Subjects

We included a total of 30 subjects in this study (37 subjects met the inclusion criteria but 7 were excluded due to incomplete data).

Inclusion criteria were as follows: (1) PWE who had at least two TDM reports, (2) at least a three-month interval between the two reports and (3) during the first sampling, the seizure had to be uncontrolled (having at least one seizure before the sampling in the preceding months).

Exclusion criterion was insufficient data on the TDM request form (including age, gender and seizure frequency).

Effectiveness Measures

The effectiveness measures employed by Salih et al. (2013), the number of patients that achieved $\geq 50\%$ reduction in seizure frequency and the number of patients with 3-month seizure free period, were used in this study. The seizure control of patients were classified into uncontrolled (defined as no change or increase in seizure frequency), controlled (seizure frequency reduction of at least 50%) and complete seizure remission according to the number of seizures self-reported by the patient. The seizure frequency

was recorded as average number of seizure per month. If this was not feasible, the seizure frequency was the number of seizure experienced in the preceding month before blood sampling. For statistical analysis, the seizure control patients were categorized into controlled or uncontrolled only.

Statistical Analysis

The normality of all continuous variables were tested using the Shapiro-Wilk test. Further confirmation of normality was achieved via inspection of histogram.

We expressed normally distributed socio-demographic continuous variables as mean $\pm$ SD. Non-normally distributed continuous variables were reported as median (IQR). All nominal data were expressed as frequency and percentages.

The association of number of recommendation accepted and seizure control was analysed using Fischer's exact test and Phi coefficient reported if the result was statistically significant.

We also reported the odds ratio of controlled seizure when pharmacist's recommendation was accepted.

Ethical Approval

Ethical clearance was obtained from the Medical Research & Ethics Committee, Ministry of Health Malaysia [(5)KKM/NIHSEC/P15-1050].

RESULTS

Demographic Data

The demographic data of the subjects are presented in Table 1. All patients had been taking the specified AEDs for at least 6 months before the study. There were more males than females and 2/3 of the subjects were on monotherapy.

Outcome after TDM

A total of 17 (56.67%) subjects had their seizure frequency decreased by at least 50% after TDM. 11 (36.67%) subjects achieved total remission after TDM.

Total number of tests were 41 on both visits. There was an increase of 7.32% in the number of drug concentration within the predefined reference range after TDM (Figure 1).

Relationship between Accepted Recommendation and Seizure Control

Out of the 30 recommendations given, 24 were accepted with an acceptance rate of 80%. There was no statistically significant association between the number of recommendation accepted by the prescriber and the seizure control of the subjects ($p = 1.003$, Fischer's exact test).

In the group where the recommendation was accepted ($n = 24$), 58.33% achieved seizure control. In the other group where the recommendation was rejected ($n = 6$), the percentage was 50.00%. The odds ratio was 1.4, 95% CI: 0.23 – 8.42.

DISCUSSION

From our results, more than half of the subjects achieved seizure control with a majority of this group of subjects having 3-month seizure free period after the TDM service. Although the acceptance rate of the recommendations made was high, we did not find any statistically significant association between the acceptance rate and the seizure control. There was a non-statistically significant 1.4 times higher odds that pharmacist's recommendation was able to help PWE to achieve seizure control.

We found that the seizure control of subjects improved after the TDM service and most of the recommendations made were accepted by the prescribers. The improvement in seizure control is consistent with the findings from studies by Salih et al. (2013) and Rane et al. (2001) where interpretations of TDM results were provided. However, there was no association between the acceptance of recommendation and seizure control. Similarly, the odds ratio showed a modest non-statistically significant increase in the odds of achieving seizure control when pharmacist's recommendation was accepted.

Improvement in seizure control was seen with or without the acceptance of pharmacist's recommendation. We speculate that the factor causing the improvement was counselling service by the pharmacists. During the encounter with the PWE, the pharmacists might have provided motivation and reassurance, thus reinforcing the compliance in both groups of subjects.

From our findings, recommendations given by pharmacists may not be a critical factor in achieving better seizure control. Possible explanations for this observation include factors that may affect the quality of the recommendation, such as the expertise of the pharmacist, seizure type and compliance of the PWE. Different pharmacists were involved in TDM service, so the quality of the recommendation might be inconsistent as it depended on the experience and knowledge of the pharmacist. Some subjects might have seizure types that are difficult to be controlled with AEDs alone. Thus, the recommendation would have no effect on their seizure control. Another reason for the finding might be the noncompliance of the subjects. Even though noncompliance to the medications were identified during the service and the subjects had been counselled, seizure attacks due to noncompliance were still unavoidable.

Besides that, the number of subjects in both groups were not proportionate with only 6 subjects in the recommendation rejected group. This might lead to the inability to discern a difference in the outcome. Unfortunately such disproportionality was unavoidable due to high recommendation acceptance rate and prescribers' clinical judgement coinciding with the suggested recommendations.

The increase in the number of drug concentration within the predefined reference range after the TDM service is consistent with the findings by Januzzi et al. (2000). Although there was an increase in the number of drug concentration within predefined reference range, more than half of the measurements were still outside the reference range but the seizure control of more than 50% of subjects improved. This shows that predefined reference range may not be a good measure for clinical response. Individual variation means therapeutic benefit may be achieved at serum drug concentration outside these ranges (Patsalos et al. 2008). A therapeutic range which is defined as the range of drug concentrations that provide best achievable response in a given patient is advocated (Patsalos et al. 2008). Thus, the therapeutic range will differ between individuals (Patsalos et al. 2008).

In our study, the most requested AED for TDM service was sodium valproate. Due to its wide therapeutic range and the variable relation between its serum level and clinical response, it has been suggested that its dosage can be individualized on clinical grounds alone (Januzzi et al. 2000). TDM may still be valuable for phenytoin, phenobarbitone and carbamazepine for pharmacokinetics reasons (Januzzi et al. 2000; Patsalos et al. 2008; Touw et al. 2005). Nonetheless, TDM can be employed to determine the therapeutic range of a patient as a target for dosage adjustments and to identify non-compliance in the event of future seizure attacks (Patsalos et al. 2008).

From our study, it can be seen that agreement of measured drug concentrations with the reference range does not predict the seizure control. In our setting, which is the same for hospitals in Malaysia, the interval between the appointments of the PWE with doctors may be quite long. However, the PWE will have to collect their medications from the pharmacy monthly. Thus, we suggest that the pharmacists monitor the condition of the PWE during these visits to obtain an accurate picture of the progress of the PWE. By taking into account the clinical condition, a better interpretation of the measured drug concentrations and a more appropriate recommendation can be achieved.

There are a few limitations in our study. First, the sample size was small. There might be recall bias as the seizure frequency was self-reported by the subjects. Besides that, the seizure type of the subjects were not recorded. Some seizure types are inherently more difficult to control and this might lead to an underestimation of the value of TDM.

CONCLUSION

Our study showed that a pharmacist-managed TDM service is able to improve the seizure control in more than 50% of PWE with unsatisfactory seizure control. Impactful recommendations depend on competency of pharmacists and factors such as seizure type. Instead of a standardized reference range, an individualized therapeutic range may be more valuable for the management of PWE.

ACKNOWLEDGEMENT

We would like to thank the Director of Health Malaysia for permission to publish this paper.

REFERENCES

- JANUZZI, G., CIAN, P., FATTORE, C., GATTI, G., MONACO F. & PERUCCA E. (2000) A Multicenter Randomized Controlled Trial on the Clinical Impact of Therapeutic Drug Monitoring in Patients with Newly Diagnosed Epilepsy, *Epilepsia*, 41(2): 222-230.
- PATSALOS, P. N., BERRY, D. J., BOURGEOIS, B. F. D., CLOYD, J. C., GLAUSER, T. A., JOHANNESSEN, S. I., et al. (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.
- RAHMAN, A. F. A., ABDELRAHIM, H. E. A. & IBRAHIM, M. I. M. (2013) A Survey of Therapeutic Drug Monitoring Services in Malaysia, *Saudi Pharmaceutical Journal*, 21: 19-24.
- RANE, C. T., DALVI, S. S., GOGTAY, N. J., SHAH, P. U. & KSHIRSAGAR, N. A. (2001) A Pharmacoeconomic Analysis of the Impact of Therapeutic Drug Monitoring in Adult Patients with Generalized Tonic-Clonic Epilepsy, *British Journal of Clinical Pharmacology*, 52: 193-195.
- SALIH, M. R. M., BAHARI, M. B., SHAFIE, A. A., HASSALI, M. A. A., AL-LELA, O. Q. B., ABD, A. Y., et al. (2013) Cost-effectiveness Analysis for the Use of Serum Antiepileptic Drug Level Monitoring in Children Diagnosed with Structural-Metabolic Epilepsy, *Epilepsy Research*, 104: 151-157.
- 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, *Therapeutic Drug Monitoring*, 35:183-187.
- TOMSON, T., DAHL, M. L. & KIMLAND, E. (2007) Therapeutic Monitoring of Antiepileptic Drugs for Epilepsy (Review), *Cochrane Database of Systematic Review*, 2:CD002216. DOI: 10.1002/14651858.CD002216.pub2.
- TOUW, D. J., NEEF, C., THOMSON, A. H. & VINKS, A. A. (2005) Cost-Effectiveness of Therapeutic Drug Monitoring: A Systematic Review, *Therapeutic Drug Monitoring*, 27(1): 10-17.
- WATSON, I., POTTER, J., YATSCOFF, R., FRASER, A., HIMBERG, J. J. & WENK, M. (1997) Therapeutic Drug Monitoring, *Therapeutic Drug Monitoring*, 19: 125.

Table 1: Demographic data (n=30).

Age [year, median (IQR)]	23 (16.25, 32.75)
Gender [frequency (%)]	
Male	20 (66.67%)
Female	10 (33.33%)
Number of antiepileptic drugs [frequency (%)]	
1	20 (66.67%)
2	8 (26.67%)
3	2 (6.66%)
Type of antiepileptic drug [frequency (%)] ^a	
Carbamazepine	5 (16.67%)
Lamotrigine	3 (10.00%)
Phenobarbitone	1 (3.33%)
Phenytoin	7 (23.33%)
Sodium valproate	26 (86.67%)

^aTotal percentage was greater than 100% as some subjects were taking more than one antiepileptic.

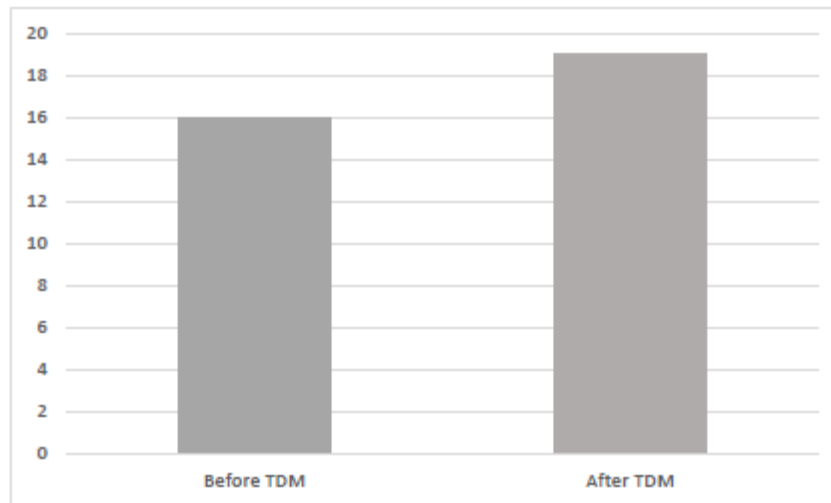


Figure 1: Number of drug concentration within predefined reference range before and after TDM.