SJP Sarawak Journal of Pharmacy

Journal Homepage: http://jknsarawak.moh.gov.my/spj/

Appropriateness of Therapeutic Drug Monitoring Request of Valproic Acid for Inpatient and Emergency Department Patients in Sibu Hospital

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ABSTRACT

Introduction: Therapeutic drug monitoring (TDM) refers to the individualisation of dosage by maintaining plasma or serum drug concentrations within a target range. The World Health Organisation (WHO) proposed categorising valproic acid (VPA) to be of lower priority among the listed drugs for TDM. However, VPA is one of the most commonly analysed assays in Sibu Hospital. This study aimed to evaluate the appropriateness of therapeutic monitoring of VPA in Sibu Hospital. The results from this study will help to better understand the various indications for VPA sampling in the hope to reduce unnecessary VPA TDM requests in the future.

Methods: This was a retrospective cross-sectional clinical audit that included the VPA TDM requests for inpatient and emergency department patients in Sibu Hospital. Data were retrieved from VPA TDM forms from 1st January to 31st December 2020 and case notes. The collected data included demographic characteristics, antiepileptic drug (AED) information, indications and sampling time of VPA TDM requests, pharmacist's recommendation, and prescriber's acceptance, which were then analysed using SPSS version 22.

Results: A total of 97 VPA TDM requests for 61 patients were included in the clinical audit. The majority (90.7%) of the requests came with appropriate indications and almost half of the VPA TDM samples were taken at the appropriate timing. Pharmacists proposed dose increments for half of the requests with subtherapeutic drug levels. Around three quarters (72.2%) of pharmacists' recommendations were accepted by prescribers.

Conclusion: We concluded that the majority of VPA TDM requests had appropriate indications. Unfortunately, half of these requests were sampled incorrectly, limiting valuable recommendations on dose adjustments. Measures should be taken to ensure VPA TDM are ordered with appropriate indications and accurate sampling time in order to optimise the service.

Keywords: Therapeutic Drug Monitoring, Valproic Acid, Clinical Audit

INTRODUCTION

Therapeutic drug monitoring (TDM) refers to the individualisation of dosage by maintaining plasma or serum drug concentrations within a target range. Therapeutic drug monitoring is indicated in a variety of scenarios; for dose adjustment, to determine the adequate loading dose (after starting phenytoin treatment), to assess compliance (antiepileptic concentrations in patients having recurrent seizures) and for diagnosing or avoiding toxicity (when patient is prescribed with aminoglycosides or cyclosporin) (1).

The World Health Organisation (WHO) proposed that TDM should be prioritised for aminoglycosides, phenytoin and lithium, as these drugs have very narrow therapeutic range and TDM was useful even for non-critically ill patients. Meanwhile, TDM of Vancomycin, Methotrexate and Cyclosporine were considered beneficial in patients with concomitant treatments or comorbidities such as liver or kidney failures. As for digoxin, phenobarbital, carbamazepine and valproic acid (VPA), it was concluded that there were no differences between patients with and without TDM, as careful clinical assessment was enough in most cases, hence TDM for these drugs were of little significance (1).

TDM service has been available in Sibu Hospital since 1998. There are nine assays that can be monitored in Sibu Hospital, namely Vancomycin, Gentamicin, Amikacin, Acetaminophen, Methotrexate, Cyclosporine, Phenytoin, Carbamazepine and VPA. Other than requests from Sibu Hospital, samples from district hospitals and health clinics from the central zone of Sarawak are sent to Sibu Hospital for analysis as well.

In 2020, a total of 1773 tests were analysed in Sibu Hospital. Among the nine assays, Vancomycin was the most frequently analysed, with a total of 378 tests, followed by VPA (368 tests) and Gentamicin (360 tests). An allocation of RM 160,000.00 was used to purchase TDM reagents in 2020. The fund used to purchase reagents for antiepileptics were RM 28,548.00 for VPA, RM 17,536.00 for Phenytoin and RM 8,952.00 for Carbamazepine.

There were concerns that resources spent on TDM may be wasted as there were many published observations of inappropriate measurements of antiepileptic drugs (2-4). Moreover, there has not

been any evaluation of TDM practice in this hospital. This study aimed to evaluate the appropriateness of therapeutic monitoring of VPA in Sibu Hospital as it is the most commonly analysed antiepileptic despite being categorised as low priority for TDM by WHO. The results from this study can serve as a reference to better understand the indications for VPA sampling which in turn may help to reduce unnecessary VPA TDM requests in the future.

METHODS

This was a retrospective cross-sectional clinical audit to evaluate the appropriateness of therapeutic drug monitoring requests for VPA in Sibu Hospital. All the VPA TDM request forms from 1st January to 31st December 2020 were retrieved. Requests for inpatient and emergency department patients were included for this clinical audit. Patient's information was gathered from TDM request form which include: age, requesting discipline, indication of VPA, VPA dose, measured level for each patient and pharmacists' recommendation on each TDM. Patient's concurrent medication was retrieved from both TDM request form and case notes. Meanwhile, patient's case notes were referred to gather information on whether there were dose changes in VPA according to the pharmacist's recommendation. The therapeutic range of VPA at steady state for epilepsy and psychiatric disorder were defined as 50 - 100 mcg/ml and 50 - 125 mcg/ml, respectively. Appropriateness criteria for indication and sampling times were adapted from Hamzah et al. (4).

Table 1: Indication and sampling criteria for VPA (4)

Appropriate Indication	**Appropriate Sampling**
• As initial monitoring • No or inadequate response • Suspected drug interaction • After a change in dose regimen • Within 6 hours after seizure recurrence • Suspected non-compliance	At steady state (at least 2-4 days after initiation or change in dose regime) AND within 2 hours before next dose
• Suspected toxicity	Anytime, if repeated, should not be less than one half-life of the previous sample.

In TDM request forms, indications of request were divided into four sections, namely therapeutic monitoring, suspected toxicity, non-compliance and others. If therapeutic monitoring or others was selected, more information was retrieved from the request form or case notes to determine if it fits into the criteria mentioned in Table 1. For requests with indications other than suspected toxicity, appropriate sampling time was defined as samples taken at steady state and within 22 to 24 hours post dose in the patients with 24 hourly (OD) dosing; within 10 to 12 hours post dose in patients with 12 hourly (BD) dosing; within 6 to 8 hours post dose in patients with 8 hourly (TDS) dosing. The interval between last VPA dose and blood sampling were recorded to decide if the sampling time was appropriate. For repeated samples of suspected toxic cases, the interval between two samples were recorded. The population half-life from Clinical Pharmacokinetic Handbook Malaysia, as shown in Table 2 was referred (5). The data collected were analysed using SPSS version 22. Descriptive statistics were used to summarise the data. Discrete variables were presented in frequency and percentage, while continuous variables were presented in mean (standard deviation, SD) for data with normal distribution or median (interquartile range, IQR).

Table 2: Population half-life of VPA (5)

	Monotherapy	**Polytherapy**
Paediatric	6 – 8 hours	4 – 6 hours
Adult	12 – 18 hours	4 – 12 hours

The study was registered with National Medical Research Register (NMRR-21-19-57959 (IIR) and ethical approval was granted by Malaysian Research Ethics Committee on 2nd February 2021, KKM/NIHSEC/P21-168 (4).

RESULTS

A total of 368 VPA TDM requests were received in 2020. Of these, 251 requests were excluded from the clinical audit as those were requests from other district hospitals or health clinics from the central zone of Sarawak; requests for outpatients in Sibu Hospital and requests with incomplete details. Therefore, only a total of 97 VPA TDM requests for 61 patients were included in the clinical audit.

Patient's characteristics

Patients' ages ranged from 2-88 years with mean age 39.3 (SD = 18.42) (Table 3). There were more male patients (62.3%) compared to female patients (37.7%).

Table 3. Characteristics of patients

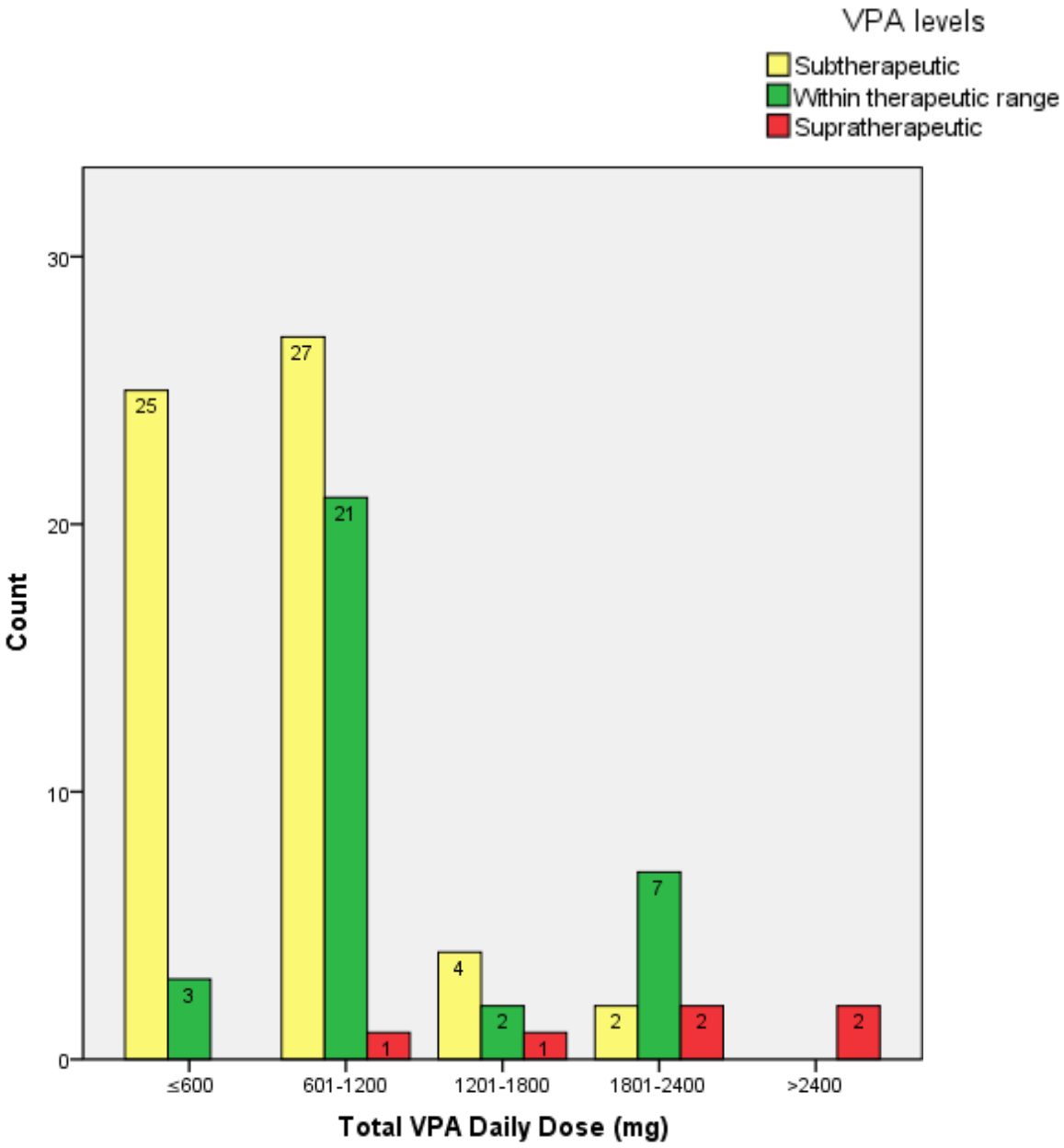
Demographic Details	Number of patient (n=61)	Percentage (%)	Mean (Standard Deviation)
Age (years)			39.26 (18.42)
<18	6	9.8	
18-30	15	24.6	
31-50	22	36.0	
51-70	14	23.0	
>70	4	6.6	
Gender			
Female	23	37.7	
Male	38	62.3	

Among the 97 requests, the majority were requested by the Department of Internal Medicine (32.0%) & Emergency & Trauma (30.9%). The median total VPA daily dose was 1000 mg (ranged from 150 mg to 10,000mg). More than half (56.7%) of the requests were made when patients were on VPA monotherapy, while the remaining were on multiple antiepileptics (Phenytoin, Carbamazepine, Levetiracetam, Phenobarbitone, Topiramate, or Clobazam). Only 34.0% of the requests were within therapeutic range (Table 4). For requests with a total daily VPA dose of 600mg or less, only 10.7% of the requests were within therapeutic range. As for VPA requests for patients with a total daily VPA dose ranging between 601 – 1,200 mg, 42.9% of the requests were within therapeutic range (Figure 1).

Table 4. Descriptive of VPA TDM Requests

	Number of request (n=97)	Percentage (%)	Median (Interquartile Range)
Requesting Department			
Internal Medicine	31	32.0	
Emergency & Trauma	30	30.9	
Neurosurgical	18	18.6	
Anaesthesiology	7	7.2	
Psychiatry	6	6.2	
Paediatrics	3	3.1	
Surgical	2	2.1	
Total VPA Daily Dose (mg)			1000 (600)
≤600	28	28.9	
601-1200	49	50.5	
1201-1800	7	7.2	
1801-2400	11	11.3	
>2400	2	2.1	
VPA Monotherapy			
Yes	55	56.7	
No	42	43.3	
VPA level			
Subtherapeutic	58	59.8	
Within therapeutic range	33	34.0	
Supratherapeutic	6	6.2	

Figure 1: Total VPA daily dose (mg) Vs VPA level



Appropriateness of indication of VPA TDM requests

VPA TDM were ordered based on various indications. The majority (90.7%) of the requests came with appropriate indications. Most of the requests that were deemed to be inappropriate were due to them being requests for non-compliance despite patients had only been stabilised and the original VPA dose had only been resumed or in patients who had been on maintenance dose for a certain period of time but presented with good clinical response to AED therapy (Table 5).

Table 5. Appropriateness of indication of VPA TDM requests

	Number of Requests (n=97)	Percentage (%)
Indication		
As initial monitoring	12	12.5
After a dose change	14	14.4
No or inadequate response	10	10.3
Within 6 hours after seizure recurrence	29	29.9
Suspected toxicity	9	9.3
Suspected non-compliance	13	13.4
Suspected toxicity and non-compliance	1	1.0
None that fit the appropriate indication criteria in Table 1	9	9.2
Appropriate Indication		
Yes	88	90.7
No	9	9.3

Appropriateness of sampling time of VPA TDM requests

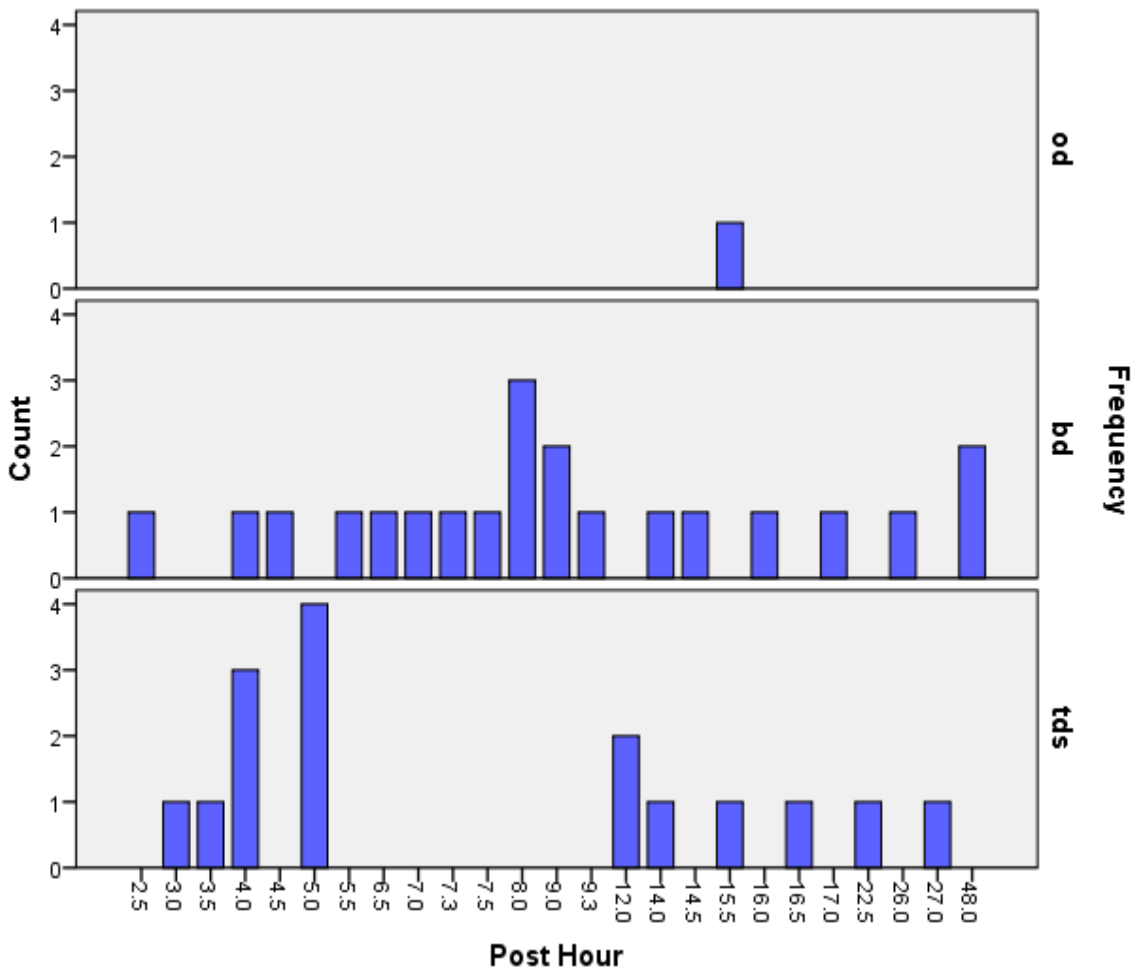
Almost half (49.5%) of the VPA TDM samples were taken at the appropriate time, while 9.3% of the requests were with unknown timing of the last dose as the patients were intubated, hence history taking could not be performed (Table 6). Among the 40 requests with inappropriate sampling time, 4 samples were taken before steady state was achieved. Meanwhile, there were 38 samples that were not taken within 2 hours before the next dose.

Table 6. Appropriateness of sampling time of VPA TDM requests

Appropriate Sampling Time	**Number of Requests (n=97)**	**Percentage (%)**
Yes	48	49.5
No		
Before steady state but within 2 hours before the next dose	2	2.1
Before steady state and not within 2 hours before the next dose	2	2.1
At steady state but not within 2 hours before the next dose	36	37.0
Unknown	9	9.3

The inappropriate sampling time based on interval from last VPA dose ranged from 2.5 - 48 hours (Figure 2). 13 out of 38 samples were taken less than 6 hours post-dose. 25.0% of the samples for patients with BD dosing were taken less than 10 hours post-dose whereas 12.5% of them were taken later than the correct sampling time. In addition, for patients with TDS dosing, 24.0% of the samples were taken less than 6 hours post dose, and 19.0% of them were taken more than 8 hours post-dose.

Figure 2：Inappropriate sampling time based on interval from last VPA dose (n=38)



Impact of TDM Results on patient's management

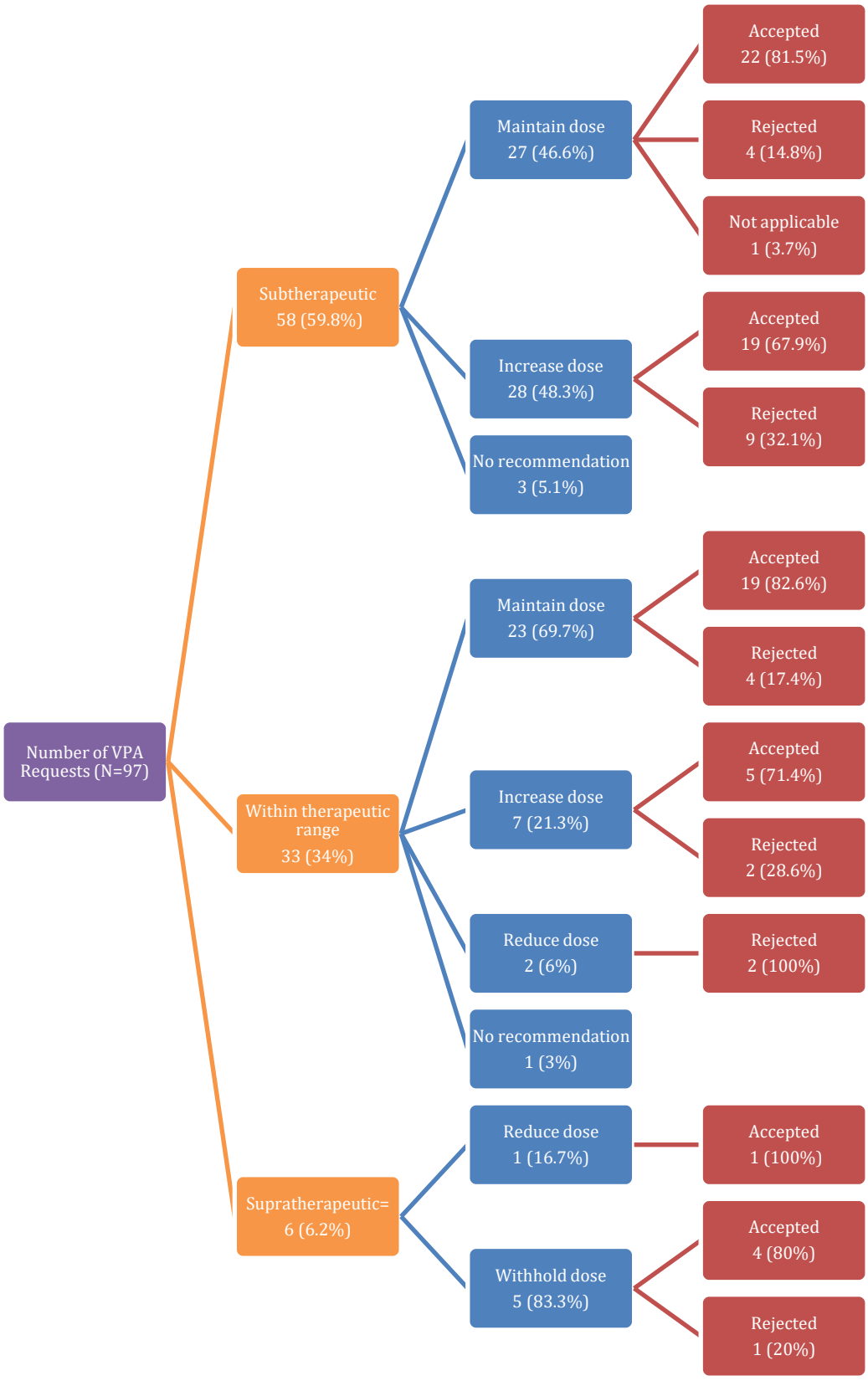
Out of 51.5% of the VPA TDM requests, pharmacists recommended maintaining the current dose. Pharmacists proposed dose increments for half of the requests with subtherapeutic measured levels. Pharmacists suggested to withhold the dose for requests with supratherapeutic VPA levels. In four cases, no recommendations were done by pharmacists as the VPA doses were adjusted by prescribers before VPA levels were available (Table 7). Of all the pharmacists' recommendations, 72.2% were accepted by prescribers. Five VPA TDM results were not appreciable as dose adjustment was done before VPA results was available or patient passed away after result was available.

Table 7: Impact of TDM results on patient's management

	Number of Requests (n=97)	**Percentage (%)**
Recommendation by Pharmacist		
Maintain dose	50	51.5
Increase dose	35	36.1
Withhold dose	5	5.2
Reduce dose	3	3.1
No recommendations	4	4.1
Recommendation accepted by prescriber?		
Yes	70	72.2
No	22	22.7
Not applicable	5	5.1

Pharmacists proposed dose increments for almost half (48.3%) of the requests with measured subtherapeutic levels (Figure 3). However, only 67.8% of these suggestions were accepted by prescribers. Apart from that, pharmacists suggested to maintain the dose of approximately 70.0% of the requests with VPA levels within therapeutic range and majority of these recommendations were accepted. Pharmacists recommended to either reduce or withhold the next dose for all the requests with supratherapeutic levels but prescriber chose to maintain the dose for one instance.

Figure 3: VPA levels vs Recommendations by pharmacist vs Prescriber's acceptance



DISCUSSION

One of the rules for the use of TDM in AED therapy is to request the measurement of serum AED concentrations only when there is a clear clinical question (6). In our clinical audit, 90.7% of the VPA TDM requests were categorised as with appropriate indications. Other studies had reported a highly variable percentage of compliance, ranging from 15.0% to 73.0% (2,3,7). However, these studies set the appropriateness criteria based on the guidelines from their respective countries. The most noticeable difference was with Rathmalgoda et al. with appropriate indication in only 15.0% of VPA TDM requests assessing compliance and toxicity (7).

The indications of VPA TDM requests from our audit were mainly for therapeutic monitoring, followed by requests for suspected non-compliance and suspected toxicity cases. Covanis et al. reported that in patients more than 21 years old with VPA monotherapy, the mean daily dose of 21 mg/kg VPA and a mean serum concentration of 83 mcg/ml were sufficient for patients to be seizure free (8). The same study suggested that VPA TDM was only indicated when the total daily VPA dose was more than 2.6 g. On the other hand, Gram et al. concluded median daily dose of 3 g/day and a median serum concentration of 45 mcg/ml were needed in patients with multiple AED to get a superior clinical effect (9). In Malaysia, the recommended starting dose of VPA for adult was 600 mg/day for epilepsy and 1g for psychiatric disorders, which could be titrated to usual maintenance dose of 1-2 g/day (20-30 mg/kg/day) (10). From the findings of our audit, the majority of requests with total daily VPA doses of 600 mg or less were found to be subtherapeutic.

Another fundamental element of TDM for AED is that the interpretation of serum AED concentrations must take into consideration the interval between the last ingested dose and the expected pharmacokinetic profile of the AED being monitored (6). Only 49.5% of the VPA TDM requests from our audit met the criteria for appropriate sampling time. Similarly, other studies have reported a highly variable percentage of compliance to appropriate sampling time, ranging between 29.0%-80.0% as the criteria was set based on the practices in the respective countries (2,3,7). Both Schoenenberger et al. and Affolter et al. pre-defined appropriate sampling time as samples taken after achieving steady state and at trough level, but these were not applicable for samples taken after seizure occurrence and suspected toxic cases (2,3). Meanwhile Rathmalgoda et al. considered samples taken at least 8 hours after VPA dose valid (7).

The oral bioavailability of standard formulations of VPA is almost 100.0% regardless of meal, while time to reach maximum plasma concentration vary. Time to peak for VPA usually occur within 2-3 hours for syrup, between 3-5 hours (delayed further by food intake) for enteric-coated tablets and between 5-10 hours for sustained release formulations (11). Half-life of VPA is relatively short (12-18 hours), and even shorter in patients with multiple AED (5). The distinct pharmacokinetic profile of VPA attributes to the large fluctuation of serum VPA concentration throughout the day (12). Ideally, samples for VPA monitoring should be drawn before the morning dose, which may not be practical in clinical setting (6). Nevertheless, random VPA TDM levels are often uninterpretable. From our findings, the inappropriate sampling time based on interval from the last VPA dose ranged between 2.5 - 48 hours. 13 out of 38 samples were taken less than 6 hours post-VPA dose. Samples taken less than 6 hours after VPA dose will be falsely high, as VPA are still in the absorption phase, resample is often needed to get the true trough level. Meanwhile, 12.5% of the samples for patients with 12 hourly dosing were taken later than the correct sampling time; whereas for patients with 8 hourly dosing, 19.0% of them were taken more than 8 hours post-dose. Random samples taken after missed doses will be falsely low, which give no added value to the clinical management. It is likely that knowledge of sampling time amongst ordering clinicians may be poor. A systematic review in 2019 by Al-Roubaie et al. concluded that if optimally implemented, TDM had the potential to improve clinical care (13). These implied that correct sampling time needs to be enforced to render the TDM result more meaningful.

Suggestions for alteration in doses in our cohort were made without solely depending on the measured VPA levels. Measured subtherapeutic levels did not warrant an automatic increment in VPA dose as the interpretation of the drug concentrations should be individualised in relation to the patient's clinical response without rigid adherence to a target range (14). In these cases, causes such as poor compliance, inappropriate sampling time or drug-drug interaction should not be ruled out (5).

It was found that 72.2% of pharmacists' recommendations were accepted by prescriber. These findings were comparable to an outpatient study done by Sahil et al. in Malaysia, in which 76.0% of pharmacists' recommendations were accepted and 40.0% of the monitored levels did not result in any changes in the management (15).

The limitation of the present audit was that the assessment of indication of VPA TDM request was done retrospectively, based on the information retrieved either from the TDM request form or patient's case notes. The information gathered may not be the true indication and therefore may be misclassified.

CONCLUSION:

We concluded that the majority of VPA TDM requests were with appropriate indication but half of them were sampled incorrectly. Measures should be taken to ensure VPA TDM are ordered with appropriate indication and sampling time to optimise its use.

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