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Measuring the appropriateness of carbamazepine and valproic acid prescribing and utilization using a newly implemented online system in the Tabuk Region of Saudi Arabia

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ABSTRACT

Epilepsy is a common neurologic disorder, which is efficiently treated with carbamazepine and valproic acid. Moreover, Saudi Ministry of Health implemented a new E-system for Poison Control Centers called Awtar to enhance technology utilization in ensuring patients' satisfaction and to improve treatment outcomes. Therefore, we conducted this study to assess appropriateness of indication of requests and therapeutic levels of carbamazepine and valproic acid in Tabuk area, North West Saudi Arabia. This is a retrospective observational study conducted in Poison Control & Forensic Chemistry Center, Tabuk, Saudi Arabia. Patients' data were obtained for years 2018 and 2019. The blood levels of carbamazepine and valproic acid were measured by Therapeutic Drug Monitoring (TDM) Unit. We selected patients treated with either valproic acid or carbamazepine alone without any history of drug allergy. Data of 264 patients were extracted from Awtar E-system. Serum carbamazepine levels were within therapeutic range in 114 patients (75.50%), above-therapeutic range in 13 patients (8.61%) and sub-therapeutic levels in 24 patients (15.89%). Regarding serum valproic acid, it is within therapeutic range in 62 patients (54.87%), above-therapeutic range in 11 patients (9.73%) and sub-therapeutic levels in 40 patients (35.40%). In conclusion, this study gives information about partial appropriateness of usage of carbamazepine and low level of appropriateness of valproic acid. However, more efforts are needed to improve results of appropriateness of indication of antiepileptic drugs.

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1. Introduction

Epilepsy is one of the most prevalent neurologic disorders. It is characterized by recurrent abnormal electrical activity in certain areas of the brain called seizure. Epileptic seizures may induce

convulsion in all or some of the body muscles, resulting in loss of consciousness (Stafstrom and Carmant, 2015). Epileptic patients usually have no physical symptoms in the period between epileptic episodes. Carbamazepine and valproic acid show high efficacy in treating epileptic patients. They usually provide a good quality of life and keep patient in seizures' free status for a specific period of time. About 7 out of 10 patients have free seizure life with right use of medication (Murugesan et al., 2017). Knowledge of antiepileptic drugs' levels provides physicians with essential information that help in individualized patient therapeutic decisions and maintenance of optimal therapeutic drug concentrations (Hienke, 2016).

Carbamazepine works by maintaining normal balance of nerve activity and decreasing spread of seizure activity in brain. It has been commonly used for treatment of focal and generalized

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seizures. However, it may cause several side effects such as hyponatremia, especially in elderly patients. In addition, carbamazepine is associated with severe cutaneous adverse reactions, hematologic abnormalities, involvement of internal organs and eosinophilia (Moutaouakkil et al., 2019).

Valproic acid is widely used in treatment of epilepsy especially in children. It has multiple mechanisms of action such as blockade of sodium channels, elevation of GABA level in brain, suppression of glutamate and inhibition of T-type voltage-dependent calcium channels (Otoom and Alkadh, 1999). Toxic levels of valproic acid can result in central nervous system depression, hyperammonemic encephalopathy, hepatotoxicity, pancreatitis, acute renal injury, respiratory depression, metabolic acidosis, electrolyte imbalance and blood dyscrasias (Cutshall et al., 2017).

Despite of using standard doses of antiepileptic drugs in treating patients, individual variability affects serum concentration of these drugs leading to wide diversity responses of patients to the same dose of therapeutic agents. During the last two decades, therapeutic monitoring of drugs, especially antiepileptic drugs, produced marked effects on epilepsy management and significantly reduced the number of epileptic episodes as it enhances the understanding of pharmacokinetics properties of antiepileptic drugs (Patsalos et al., 2018). In addition, knowledge of drug levels inside patients' body provides important information for therapeutic decision-making and to avoid adverse reactions. Therefore, therapeutic levels of antiepileptic drugs are frequently used to evaluate patient compliance to therapy, minimize medication-induced toxicity and maximize seizure control (Dalaklioglu, 2013). The major problem takes place in huge hospitals, which have high staff turnover leading to reduction in evaluating the appropriateness of antiepileptic drugs (Hanin et al., 2017).

In order to increase the utilization of cutting-edge technologies, to outline responsibilities and to guarantee confidential performance, Saudi Ministry of Health introduced Awtar program. The program greatly provides twenty-one integrated electronic solutions for filing of patients' data and documentation of procedures. It started by physician request, pathing through analysis and ends with electronic reports. It accelerated the performance of poison control centers. The program achieved the prize of best innovative digital platform in Saudi Arabia in the field of health and welfare in 2018. We aimed to get the benefits of the newly implemented Awtar program in searching patients' files for the therapeutic drug monitoring of carbamazepine and valproic acid requests in last two years. We also aimed to evaluate the appropriateness of indication and therapeutic levels of both carbamazepine and valproic acid prescribed for patients with epilepsy in Tabuk area in North West of Saudi Arabia.

2. Methods

2.1. Study design

This is a retrospective observational study. The blood levels of carbamazepine and valproic acid were measured in the Poison Control & Forensic Chemistry Center. The Center is responsible for measuring the Therapeutic Drug Monitoring (TDM) for all hospitals in Tabuk area, North West of Saudi Arabia.

2.2. Ethical approval

The protocol of the study was approved by the Institutional Review Board in General Directorate of Health Affairs in Tabuk Region under IRB protocol number TU-077/019/016 and registration number H-07-TU-077.

2.3. Subjects

Patients' files were selected according to the following inclusion criteria; patients treated with either valproic acid or carbamazepine alone without any history of their allergy. Patients' files were excluded if they had uncontrolled complications, multi-organ failure, hepatic disease and renal disease. In addition, pregnant and breastfeeding female patients were also excluded.

2.4. Analysis of serum carbamazepine and valproic acid values

Collection of blood samples from hospitals and their transfer to Poison Control & Forensic Chemistry center were done according the following protocol. Random blood samples were collected from patients under supervision of their physicians in their corresponding hospital. Samples were refrigerated at 4 °C in biohazard labeled specimen bag and were transferred inside medical cool boxes to Poison Control & Forensic Chemistry Center for further assessment of samples. Serum concentrations of carbamazepine and valproic acid were determined by chemiluminescent micro-particle immunoassay (CMIA) using Architect from Abbott Laboratories (Abbott Park, Illinois, USA).

2.5. Data collection by poison control E-system (Awtar)

The search and selection of patients' files was done using Poison Control E-System (Awtar), which facilitates the searching process and help greatly in checking the inclusion and exclusion criteria in patients. Data was obtained from patients' files covering TDM analysis conducted in 2018 and 2019. The data were collected from patients' electronic records. They include demographics (age, gender, weight and height), symptoms, medication dosage, route of administration, sample collection type, request indication, serum levels of carbamazepine and valproic acid, clinical responses and dose alteration.

2.6. Appropriateness criteria

The aspects of appropriateness criteria include appropriateness of indication for requests of therapeutic drug monitoring and appropriateness of therapeutic drug levels. The indications of requests were considered appropriate when performed to check patients' compliance, to investigate patients with no response, to insure suspected toxicity and to help dose or drug change decision. The requests were considered inappropriate, if there is no clear indication.

2.7. Statistical analyses

The results were represented as number and percent and as mean \pm standard error. Variables were compared by one way ANOVA followed by Tukey test correction test if the difference is significant. All analyses were done on a personal computer using SPSS program version 20. P value < 0.05 was considered statistically significant.

3. Results

3.1. Patients' characteristics

After collecting all patients records from Poison Control & Forensic Chemistry Center in Tabuk, Saudi Arabia for years 2018 and 2019, we found only 264 patients achieved the inclusion criteria. Out of these patients, 151 patients were treated with carbamazepine and 113 patients were treated with valproic acid.

About 46% of patients treated with carbamazepine were male with mean age 29.64 years. They received a mean dose of 285 mg/day of carbamazepine and showed mean serum level of 6.56 µg/ml. Regarding valproic acid, 50.4% of patients were male with mean age of 27.02 years. They received a mean dose of 501 mg/day of valproic acid and showed mean serum level of 60.8 µg/ml (Table 1).

Poison Control & Forensic Chemistry Center in Tabuk performed therapeutic drug monitoring for several drugs and serves for many hospitals in the area. The distribution of TDM patients' request according to the hospitals in the area was summarized in Table 2. We want to acknowledge the help of Awtar system in collecting these patients' files. In the past, collecting these files required the research team to search for TDM data in each hospital by digging in tons of paper files with many missing information about patients characteristics.

3.2. Therapeutic levels of antiepileptic drugs

We used the reference therapeutic range (4–10 µg/ml) for carbamazepine and the reference range (50–100 µg/ml) for valproic acid for determination of distribution of TDM results as sub-therapeutic, therapeutic or above therapeutic levels, according to data provided by the manufacturer and local population-based ranges.

We found 75.5% of carbamazepine samples were within the therapeutic range. The percent of female patients within the therapeutic range (82.7%) were higher as compared with male patients (67.14%). Regarding valproic acid, 54.87% of TDM samples were within the therapeutic range. The percent of male patients (59.65%) within the therapeutic range were higher than female patients (50%) do (Fig. 1a). Next, we classified patients according to their age to young (<18 years) and adult (more than 18 years). In patients treated with carbamazepine, majority of young patients has sub-therapeutic levels (52.94%), while majority of adult patients have normal therapeutic levels (79.85%). Regarding valproic acid treatment, majority of patients has normal therapeutic levels; 48.15% in young patients and 57% in adult patients (Fig. 1b).

The therapeutic plasma levels of antiepileptic drugs in patients were presented in Table 3. According to results of carbamazepine, there was no statistically significant differences in sub-therapeutic or therapeutic plasma levels between the two genders. In the above therapeutic levels, female patients showed significant increased plasma carbamazepine as compared with male patients. Regarding valproic acid, there was no statistically significant differences in sub-therapeutic and above-therapeutic plasma levels between the two genders. However, in the group within therapeutic plasma levels, female patients showed significant elevation in valproic acid as compared with the male group.

In parallel, when we classified patients according to their age as represented in Table 4. However, after comparing patients' data we did not find any significant differences in both drugs in relation to their age group.

Table 1
Summary of study patients:

Variable	Carbamazepine (n = 151)	Valproic acid (n = 113)
Gender male, n (%)	70 (46.4%)	57 (50.4%)
Gender female, n (%)	81 (53.6%)	56 (49.6%)
Age, mean ± SE, years	29.64 ± 0.76	27.02 ± 1.13
Dose, mean ± SE (range), mg/day	285.53 ± 12.62 (60–1000)	501.77 ± 32.54 (100–1500)
Blood level, mean ± SE (range), mg/l	6.56 ± 0.24 (0.01–16.75)	60.80 ± 2.77 (0.01–131.77)

Table 2

The distribution of antiepileptic drugs TDM assay requests according to the hospital.

Hospital	Carbamazepine (n = 151)	Valproic acid (n = 113)
King Fahd Specialist Hospital	2 (1.3%)	0 (0%)
King Khaled Civil Hospital	37 (24.5%)	32 (28.3%)
Al-Amal Complex for Mental Health	1 (0.7%)	2 (1.8%)
Clinics Rehabilitation Centers	110 (72.8%)	75 (66.3%)
Alwajah Hospital	1 (0.7%)	3 (2.7%)
Maternity and Children Hospital	0 (0%)	1 (0.9%)

3.3. Appropriate indication antiepileptic drugs requests

Fig. 2a represented the appropriateness of indication for antiepileptic drugs requests. Appropriate indication of carbamazepine requests were 55.63%. The percent of appropriate indication request in male patients (70%) was high as compared with the female patients (43.21%). In case of valproic acid, the appropriate indication requests were 73.45%. The appropriate indication of valproic acid requests were similar between male and female patients. When we classified patients according to their age, in carbamazepine treated patients, 88.24% of indications are appropriate in young patients and the appropriate indications in adults was 51.49%. Regarding patients treated with valproic acid, they results were almost similar 77.78% appropriate indication in young patients and 72.09% appropriate indication in adult patients (Fig. 2b).

The therapeutic levels of antiepileptic drugs according to appropriateness of indication of requests in relation to gender were presented in Table 5. The therapeutic levels of carbamazepine in non-appropriate requests were significantly higher than those of patients with appropriate requests in male patients and in total patients. However, therapeutic levels of valproic acid in female and total patients with non-appropriate requests were higher than those with appropriate requests do.

Finally, we classified patients according to appropriateness of indication in relation to age group. We found no significant difference in serum levels of both drugs between appropriate and none appropriate indication except for adult patients treated with valproic acid. We found serum levels of valproic acid in adult patients with none appropriate indication is significantly higher than those of adult patients with appropriate indication (Table 6).

4. Discussion

Therapeutic drug monitoring is very essential to enhance drug action, to prevent its adverse effects and to promote the concept of individualize drug treatment. In addition, interventions are essential to enhance the appropriateness of antiepileptic drugs usage. Therefore, we conducted this study in North West area of Saudi Arabia to investigate the appropriateness of indication and therapeutic drug levels of both carbamazepine and valproic acid. We used TMD data from Poison Control & Forensic Chemistry Center. We excluded patients with uncontrolled complications, hepatic disease, renal disease and both pregnant and breastfeeding female patients to prevent to remove any effect that may influence the results of our study (Ratanajamit et al., 2009).

Carbamazepine is the most frequently requested antiepileptic drug in hospitals inside North West Saudi Arabia. More than of 75.5% of patients treated with carbamazepine has normal therapeutic levels, while in patients treated with valproic acid, the percent of patients with normal therapeutic levels was as low as 54.87%. Therefore, according to TDM results, we can conclude that carbamazepine monitoring seems to be generally more successful than valproic acid. It has been reported previously that valproic

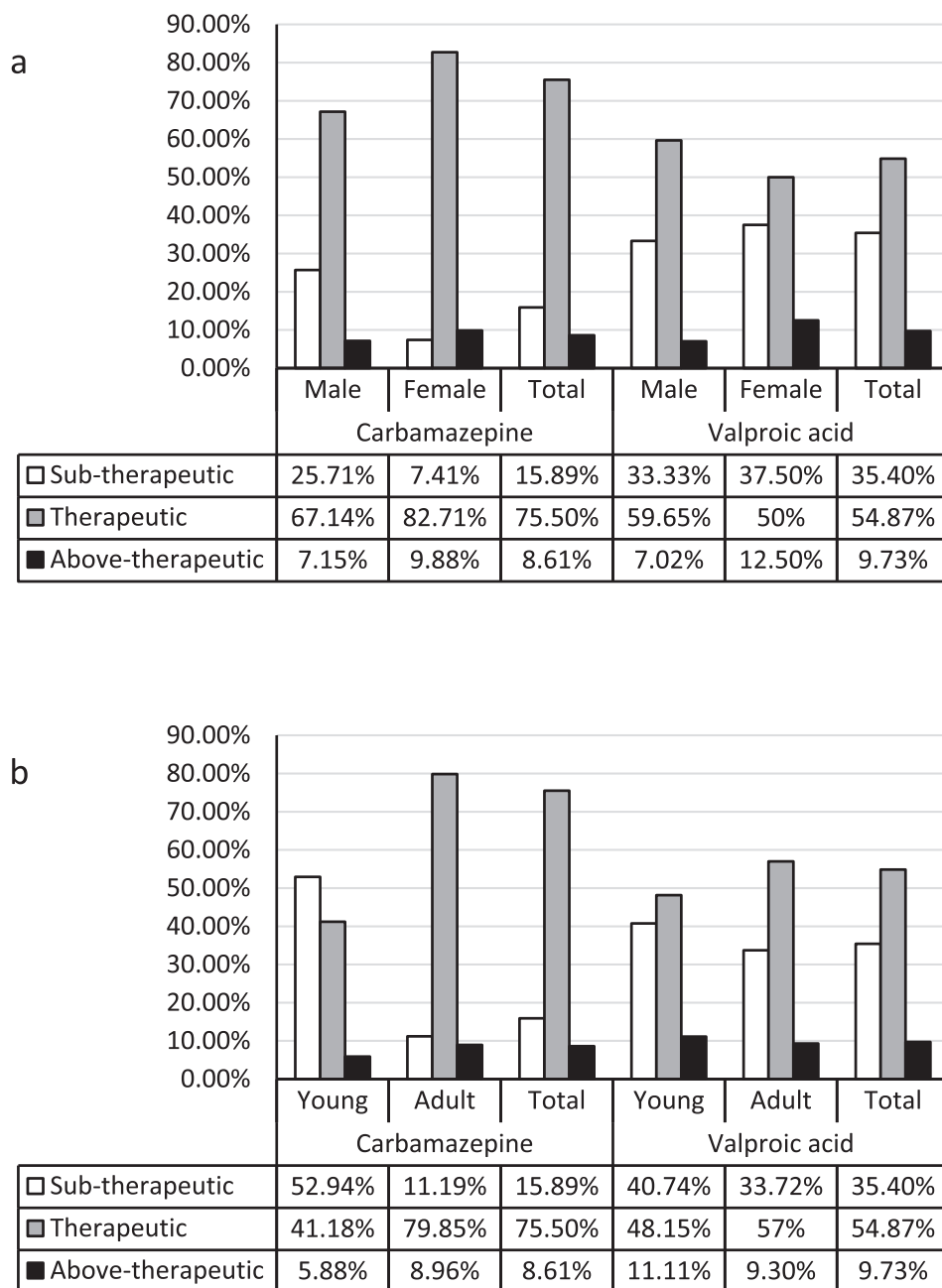


Fig. 1. Percent distribution of sub-therapeutic, therapeutic and above-therapeutic levels of therapeutic drug monitoring assays for carbamazepine and valproic acid in respect to the gender of patients (a) and age group (b).

Table 3

Therapeutic levels of the antiepileptic drugs ($\mu\text{g/ml}$) in relation to gender.

	Carbamazepine			Valproic acid		
	Male	Female	Total	Male	Female	Total
Sub-therapeutic level	2.38 ± 0.28	2.62 ± 0.53	2.44 ± 0.24	31.20 ± 2.02	29.01 ± 3.74	30.05 ± 2.17
Therapeutic level	6.49 ± 0.25	6.86 ± 0.18	6.71 ± 0.15	67.93 ± 2.20	$73.98 \pm 2.34^*$	70.66 ± 1.64
Above-therapeutic level	10.89 ± 0.25	$14.01 \pm 0.82^*$	12.81 ± 0.67	118.84 ± 5.29	116.06 ± 3.11	117.07 ± 2.63

* Significant as compared with male group at $p < 0.05$.

acid is relatively poorly controlled (Bowden, 2003; Dalaklioglu, 2013). In addition, our results were supported by a previous study by Sharma and colleagues in 2009, which reported good controlled therapeutic range of carbamazepine in 75.6% of the patients (Sharma et al., 2009). Out of therapeutic range, the percent of

patients with sub-therapeutic level is higher than the percent of patients, which are above-therapeutic levels in both drugs. This low therapeutic levels could lead to exaggeration of epileptic episodes and elevating patients' admittances to emergency department and therefore, reduce patients' compliance and increase

Table 4
Therapeutic levels of the antiepileptic drugs ($\mu\text{g/ml}$) in relation to age group.

	Carbamazepine			Valproic acid		
	Young	Adult	Total	Young	Adult	Total
Sub-therapeutic level	2.67 \pm 0.33	2.31 \pm 0.33	2.44 \pm 0.24	27.78 \pm 3.72	30.91 \pm 2.66	30.05 \pm 2.17
Therapeutic level	6.06 \pm 0.89	6.75 \pm 0.15	6.71 \pm 0.15	72.28 \pm 2.82	70.23 \pm 1.94	70.66 \pm 1.64
Above-therapeutic level	13.65	12.74 \pm 0.72	12.81 \pm 0.67	111.09 \pm 7.23	119.31 \pm 2.32	117.07 \pm 2.63

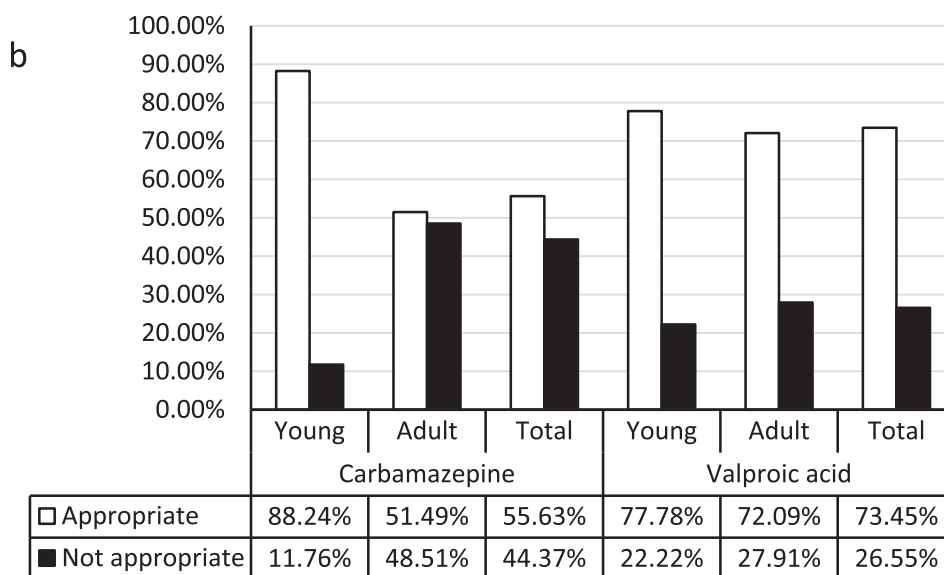
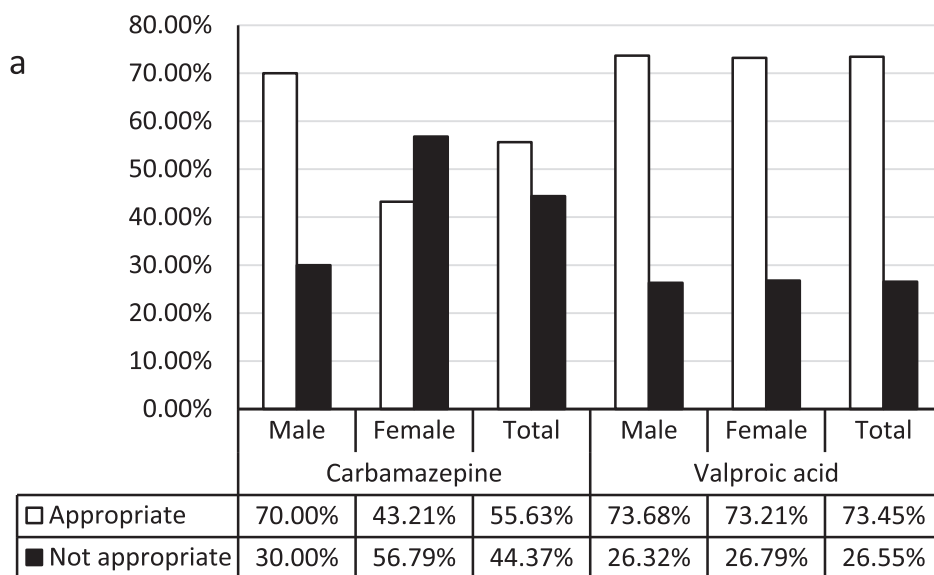


Fig. 2. The percent of appropriateness of indication for requests of carbamazepine and valproic acid in respect to the gender of patients (a) and age group (b).

Table 5
Therapeutic levels of the antiepileptic drugs ($\mu\text{g/ml}$) in relation to appropriateness of indication and gender of patients:

	Carbamazepine			Valproic acid		
	Male	Female	Total	Male	Female	Total
Appropriate	5.14 \pm 0.41	7.51 \pm 0.69	6.13 \pm 0.39	57.15 \pm 4.46	58.04 \pm 5.60	57.59 \pm 3.55
Not appropriate	7.18 \pm 0.42*	7.05 \pm 0.26	7.09 \pm 0.22*	65.17 \pm 4.35	74.21 \pm 4.01*	69.69 \pm 3.03*

* Significant as compared with those with appropriate indication at $p < 0.05$.

Table 6Therapeutic levels of the antiepileptic drugs ($\mu\text{g/ml}$) in relation to appropriateness of indication and age group of patients.

	Carbamazepine			Valproic acid		
	Young	Adult	Total	Young	Adult	Total
Appropriate	4.62 \pm 0.9	6.46 \pm 0.43	6.13 \pm 0.39	58.16 \pm 7.23	57.39 \pm 4.11	57.59 \pm 3.55
Not appropriate	5.36 \pm 0.05	7.15 \pm 0.22	7.09 \pm 0.22*	59.53 \pm 8.71	72.23 \pm 2.99*	69.69 \pm 3.03*

* Significant as compared with those with appropriate indication at $p < 0.05$.

their concern. However, clinician should be informed about these TDM results and should make more efforts for adjusting the dose of antiepileptic drugs especially valproic acid.

The serum reference ranges of both drugs in Tabuk area were adopted depending on the previous literature and according to local population-based ranges. It is important for each laboratory to calculate its own reference ranges to omit any differences between patients according to genetic diversity as well as environmental and individual variations (Dalaklioglu, 2013). Although, reference ranges for antiepileptic drugs were adopted in Tabuk area after years of analysis of patients' samples and statistical analysis of different laboratory results, it should be revised carefully on regular basis.

Many requests for antiepileptic drugs are not considered to have appropriate indication (Irshaid et al., 2004). Therefore, we checked the requests of TDM for carbamazepine and valproic acid. All physicians have to complete the requests accurately, but we found that only 55.63% of carbamazepine requests and 73.45% of valproic acid requests were appropriate. Patients with inappropriate request generally had higher serum levels of carbamazepine or valproic acid as compared with those with appropriate indication. It was reported previously that about 40% of patients requests were inappropriately indicated (Hovinga et al., 2003; Sharma et al., 2009). These results indicated that many of requests were just wasting of time and resources as well as adversely affecting clinical decision and reducing potential benefits of TDM. These inappropriate indications also affects patients' satisfaction and the state of wellbeing.

Although, this is a retrospective study, it gives important information to identify potential medication errors. The results of this study gives important information about the appropriateness of antiepileptic drugs. It will lead to many practical implications. First, TDM standard guidelines should be revised regularly according to results of appropriateness of indication and appropriateness of drugs therapeutics levels. In addition, physicians should carefully follow the revised TDM guidelines to increase patients' compliance and treatment. Improvement recommendation for the use of TDM in antiepileptic drugs should include offering efficient TDM service, physician education and encouraging cooperation and communication between physicians and clinical pharmacologists. All these efforts are needed to enhance the therapeutic effects of antiepileptic drugs and to reduce inappropriate indications. Finally, we want appreciate the conversion into using electronic systems such as Awtar, which simplified the work flow and reduced many types of errors. In addition, these electronic systems are useful in discovering medical error and help the correction actions.

5. Conclusion

This study gives information about partial appropriateness of requests of carbamazepine and low level of appropriateness of requests of valproic acid according to results of therapeutic drug monitoring. Therefore, more efforts are needed to improve the level of appropriateness of indication of antiepileptic drugs. It is

recommended to include a checklist for each request that include all important data needed for intervention and enhance appropriateness of TDM usage.

6. Ethical approval

The protocol of the study was approved by the Institutional Review Board in General Directorate of Health Affairs in Tabuk Region under IRB protocol number TU-077/019/016 and registration number H-07-TU-077.

7. Funds

None.

Declaration of Competing Interest

None.

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