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Araştırma Makalesi / Research Article

Therapeutic Drug Monitoring of Antiepileptic Drugs in Turkey: FiveYears' Experiences

Türkiye'de Antiepileptik İlaçların Terapötik İlaç Düzeyi İzlemi: Beş Yıllık Deneyim

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Abstract

Therapeutic drug monitoring (TDM) plays a major role in planning andoptimizing the treatment of a patient, as in the treatment of epilepsy. The monitoring of antiepileptic drugs (AEDs) in the management of epilepsy is crucial because of their complex pharmaco kinetic properties, narrow ther apeuticindex, and wide fluctuations. In this study, weaimed to investi gate the 5-year TDM results of AED, which is one of the mostapplied group stoour laboratory, in terms of age, genderand plasma concentrations (bytherapeutic limit). Weal so aimedto guide clinicians whodi agnose and treat epilepsy patients. This study was conducted toretros pectively analyzethe TDM results of patients in Eskişehir Osmangazi University Hospital between 2013-2018. The AED levels were classified as below, within, and above the referen cerange. The monitored drugs were valproicacid, carbamazepine, phenytoin, phenobarbital, and levetiracetam. The percent of all drug level result sanalyzed for valproicacid, carbamazepine, levetirace tamand pheno barbital was with in the referen cerange. Pheny toins howed wide fluctuation anditssub ther apeutic level was notably high. Inpractice, TDM was foundt o be helpful in the of adjust mentdrug dosage with regard to theres ponse of individual patients.

Keywords: Serum drug levels, antiepileptics, therapeutic drug monitoring.

Özet

Terapötik ilaç düzeyi izlemi (TİDİ), epilepsi tedavisinde olduğu gibi bir hastanın tedavisinin planlanmasında ve optimize edilmesinde önemli bir rol oynamaktadır. Epilepsi tedavisinde antiepileptik ilaçların (AEİ) düzeyinin izlenmesi, karmaşık farmakokinetik özellikleri, dar terapötik indeksleri ve geniş fluktuasyonları nedeniyle çok önemlidir. Bu çalışmada laboratuvarımızda en çok uygulanan gruplardan biri olan AEİ'nin 5 yıllık TİDİ sonuçlarını yaş, cinsiyet ve plazma konsantrasyonları açısından (terapötiklimtlerine göre) araştırmayı amaçladık. Ayrıca epilepsi hastalarını teşhis ve tedavi eden klinisyenlere rehberlik etmeyi amaçladık. Bu çalışma 2013-2018 yılları arasında Eskişehir Osmangazi Üniversitesi Hastanesi'ndeki hastaların TİDİ sonuçlarını retrospektif olarak analiz etmek için yapıldı. AEİ seviyeleri referans aralığı altında, referans aralığı içinde ve üstünde olarak sınıflandırıldı. İzlenen ilaçlar valproik asit, karbamazepin, fenitoin, fenobarbital ve levetirasetam'dı. Valproik asit, karbamazepin, levetirasetam ve fenobarbital için analiz edilen tüm ilaç seviyesi sonuçları yüzdeleri referans aralığındaydı. Fenitoin geniş fluktuasyon gösterdi ve terapötik düzeyi oldukça yüksekti. Uygulamada, TİDİ'nin, bireysel hastaların cevabında ayarlama yapılmasının ilacın dozajında yardımcı olduğu bulunmuştur.

Anahtar Kelimeler: Serum ilaç düzeyi, antiepileptikler, terapötik ilaç düzeyi izlemi.

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1. Introduction

Epilepsy, a common neurologic disease, affects a considerable number of people around the world (1). Anti-epileptic drugs (AEDs) are the main type of treatment for most people with epilepsy (2).

Most people with epilepsy taking AEDs are provided good seizure control and this allows them to live a normal life (3). The potential drug interactions and individual pharmacokinetics of AEDs may lead to wide fluctuations in serum concentrations and consequently clinical response; therefore, the significance of choosing the most appropriate AEDs should not be disregarded, particularly in pediatric patients (4). Furthermore, various polymorphisms (CYP2C9, CYP2C19, CYP2D6, CYP3A4, UGT1A8, and UGT2B7) also affect AED pharmacokinetics, steady-state concentration, and drug resistance, leading to possible changes in blood concentrations (5).

Therapeutic drug monitoring (TDM) is elucidated as "the use of drug measurements in biological fluids as an aid to the management of patients receiving drug therapy for the alleviation or prevention of diseases." Nowadays, in the developed world, the evolution of TDM can be passed through different stages: the development of the principles of TDM, then the automation of laboratory methods, and then the widespread expansion of the TDM (6). TDM aims at improving clinical activity, avoiding toxicity, and minimizing the costs of drug treatment (7).

TDM has a significant role in the management of epilepsy treatment and AEDs are very well suited to TDM (8). TDM means measuring the dose of blood and ensuring that the patient is protected against convulsions for as long as possible or keeping the disease under control with the minimum dose (9).

TDM began in the 1980s, and has been developed worldwide in the last 15 years (10). TDM services started in the late 1980s in Turkey, primarily in university hospitals (11). Our TDM service was opened as a part of the Department of Pharmacology at Eskisehir Osmangazi University Medical Faculty Hospital in 1988. The sharing of experiences by practitioners is necessary for effective TDM. This study shares our experience with TDM for valproic acid, carbamazepine, phenytoin, phenobarbital, and levetiracetam over a period of 5 years.

In this study, we aimed to investigate the over 5-year period TDM results of AEDs in terms of age, gender and plasma concentrations. In this way, we also aimed to provide a perspective to clinicians diagnosing and treating epilepsy patients worldwide and improve our laboratory based on these results (eg adding new AED medications to monitoring, checking therapeutic limits and planning more comprehensive research including clinical responses).

2. Material and Methods

ThisresearchwasapprovedbytheEskisehirOsmangazi Non-Interventional Clinical Research Ethics Committee (13/11/2018-09)undertheDeclaration of Helsinki. This retrospective study including the TDM data of valproic acid, carbamazepine, phenytoin, phenobarbital and levetiracetam was conducted between January 1st, 2013, and December 31st, 2017, at the Eskisehir Osmangazi University Medical Faculty Hospital, Eskisehir, Turkey. Patients included in this study were those admitted to our hospital. Blood samples were collected from pediatric and adult outpatients and inpatients. All patients were anonymized in the study, and data regarding sex (male and female), age (0-5, 5-12, 12-18, and >18 years) and range of serum drug concentrations (below-, within-, and above-reference were collected. Serum drug concentrations were measured using an Olympus AU400 Autoanalyzer with CEDIA EIAkits. The principle of this assay is for the quantitative calculation of the free drug fraction in plasma or serum. Data wereanalysedusingstatisticalpackagefortheSocialSciences SPSS Version 21.0. Descriptivestatisticswithfrequencies, mean andpercentagewereusedwhereappropriate.

3. Results

A total of 21955 AED TDM samples were evaluated during the study period. Thus, a total of 11284 patients with 21955blood samples were collected over the 5-year period. Of the 11284 patients, 56.7% were male and 43.2% were female. The percentage rate of children aged 5 years or younger was 18%, 5-12 years was 13.4%, 13-18 years was 16.0%, and 18 years or older was 52.4%. Five thousand nine hundred nineteen patients were adults (59.5% male and 40.4% female), and 5365 patients were children (53.5% boys and 46.4% girls) (Table 1).

Table 1. Age distribution of patient according to sex

Age (years)	0-5	5-12	12-18	>18	Total
Male	1184 (58.1%)	767 (50.7%)	923 (51%)	3525 (40.4%)	6399 (56.7%)
Female	854 (41.9%)	747 (49.3%)	890 (49%)	2394 (59.5%)	4885 (43.2%)
Total	2038 (18%)	1514 (13.4%)	1813 (16.0%)	5919 (52.4%)	11.284 (100%)

Of the total 21955 TDM samples, 65% were valproic acid, 14% were carbamazepine, 12%, were levetiracetam, 5% were phenytoin, and 4% were phenobarbital. Of the 14410 requests analyzed for valproic acid, 26%, 63%, and 11% were below, within, and above the reference range, respectively. A total of 2965 requests were analyzed for carbamazepine, and 24%, 63%, and 16% were below, within, and above the reference range, respectively. Of the 2568 requests analyzed for levetiracetam, 17%, 75%, and 8% were below, within, and above the reference range, respectively. Among the 1059 requests analyzed for phenytoin, 75%, 17%, and 8% were below, within, and above the reference range, respectively. A total of 953 requests were analyzed for phenobarbital, and 47%, 48%, and 5% were below, within, and above the reference range, respectively (Table 2).

Table 2. Plasma Antiepileptic Drug Level Results

Drug	Reference range (µg/mL)	Below reference (n)	Within reference (n)	Abovereference (n)
Valproic acid (65%)	50-100	3771 (26%)	9076 (63%)	1563 (11%)
Carbamazepine (14%)	4-10	715 (24%)	1860 (60%)	390 (16%)
Levetiracetam (12%)	5-40	434 (17%)	1922 (75%)	212 (8%)
Phenytoin (5%)	10-20	790 (75%)	179 (17%)	90 (8%)
Phenobarbital (4%)	15-40	449 (47%)	455 (48%)	49 (5%)

The number of TDM requests increased over the years. The increase in 2017 compared with 2013 significant. The numbers of TDM requests were 2506, 3500, 5119, 5493, and 6682 between 2013 and 2017, respectively (Figure 1).

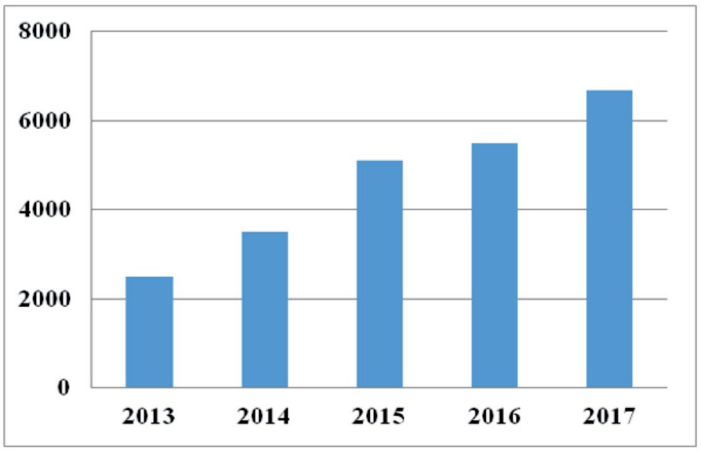

Figure 1. Number of requests for TDM in 2013 and 2017

4. Discussion

TDM has been found to be very useful in our hospital. There has been an increasing trend in the number of requests for AEDs in consecutive years (2013-2017). During this study, 21955 plasma drug concentration-measurement requests were collected over the 5-year study period. The number of TDM requests was highest for valproic acid (65%), similar to the study of Cruz et al. (12), in which the most frequently requested plasma concentrations were also for valproic acid (49.9%).

The percentage of all drug level results analyzed for valproic acid, carbamazepine, levetiracetam, and phenobarbital were within the reference range. However, among the 1059 samples analyzed for phenytoin, 75% of samples were below the reference range. Taur et al. (13) evaluated the serum level of carbamazepine, phenytoin, phenobarbitone, and lamotrigine at a tertiary care hospital, and they found similarly high rates of drug plasma levels below the reference range for phenytoin (68%). The possible causes for low plasma drug levels are noncompliance with treatment, drug interactions, quality of generic drugs, and brand substitution. However, the addition or removal of other AEDs may cause the therapeutic range to shift to the sub-therapeutic or toxic range. Another reason that may lead to changes in phenytoin serum drug levels may be its use in combination with other drugs. Drugs which may decrease phenytoin levels include: carbamazepine, chronic alcohol abuse, reserpine (14). In addition, some drugs (e.g. warfarin, sodium valproate, salicylates) could change the pharmacokinetics of phenytoin by altering its plasma protein binding, absorption or hepatic biotransformation. One of the major clinical problems resulting from such a drug interaction is the need to increase the dose, which may lead to phenytoin toxicity (15). The metabolism of phenytoin is performed by two oxidative cytochrome P450 enzymes CYP2C9 and CYP2C19. Phenytoin metabolism is decreased in people with genetic polymorphisms. The below or above reference range status may be caused by these polymorphisms, leading to slow/fast metabolizers (16, 17). As a result, it can also be suggested that a pharmacogenetic test should also be performed in laboratories.

The priority role of TDM for all AEDs is to establish a reference value in a patient by determining the optimum concentration for each patient. Our study will be beneficial in clinical practice because the daily therapeutic dose of AEDs causes different blood concentrations in each person and this could change the therapeutic response. Typically, the dose of AEDs is increased according to the clinical response.

If seizures are not managed in epilepsy, the drug level should be measured after the initiation of treatment, other medication may be added to the treatment later or the dose may be changed. The most common causes of improper AED level measurements after dosing before reaching a steady-state drug level have been determined (18). In clinical practice, limiting the drug dose and regularly monitoring drug levels helps the critical decision process in accordance with individual patient characteristics.

Intelligent interpretation of results is the most important part of TDM. Clinical pharmacologists can greatly assist physicians in ensuring proper interpretation of TDM results, through drug measurement services, as well as the individual characteristics of patients (age, sex, hepatic, kidney and heart condition, co-existing diseases and medications). Following the pharmacokinetic parameters of each patient would be more appropriate to evaluate clinical outcomes. Therefore, the development of TDM services may be beneficial in improving the treatment of patients.

There were some limitations in our study. The assessment of individual plasma drug levels was primarily based on information collected from our hospital database. However, we did not assess these data in detail because of the retrospective nature of our study. Furthermore, we did not know the factors that contributed to the TDM results because of a lack of information about the patients such as other drugs used (e.g. drug–drug interactions). Other limitations include unknown bodyweight and comorbidities, and the non-standardized time between the last dose intake and serum sampling.

5. Conclusion

In conclusion, our study may be enlightening for physicians currently performing or planning to perform TDM. However, we were very much limited by the absence of critical information such as the patient's medical history. For subsequent studies, more extensive data can be generated if patient records are obtained in collaboration with physicians.

In our hospital, TDM is a beneficial tool in epilepsy treatment to optimize the dose of AEDs according to the individual patient's needs. When the TDM is performed appropriately and patient's results are carefully interpreted, it may produce a treatment with higher efficacy, lower toxicity, and lower cost than non-TDM guided treatments. Our targets are to ensure a more common and cost-effective use of TDM and expand the range of drugs analyzed for TDM in the future.

In order to examine the effect of TDM on the clinical results of patients with epilepsy, it is necessary to conduct further studies with more detailed evaluation the patient's medical records.

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REFERENCES

1. Falcicchia C, Simonato M, Verlengia G. New toolsfor-epilepsy therapy. Front Cell Neurosci. 2018;12:147.

2. Alvarez N, Besag F, Iivanainen M. Use of antiepileptic drugs in thetreatment of epilepsy in people withintellectual disability. J Intellect DisabilRes. 1998;42:1-15.

3. Heaney DC, Sander JW. Antiepileptic drugs: generic versus branded treatments. Lancet Eurol 2007;6:465–8.

4. Iapadre G, Balagura G, Zagaroli L, Striano P, Verrotti A et al. Pharmaco kinetic sand druginteraction of antiepileptic drugs in children andadolescents. Paediatr Drugs. 2018.

5. Ben Mahmoud L, Hakim A, Ghozzi H, Atheymen R, Sahnoun Z, Zeghal K et al. Influence of ageandco-medication on the steady-state pharmaco kinetics of valproicacid in Tunisian patients with epilepsy. Rev Neurol (Paris). 2017;173:159-63.

6. Gogtay NJ, Kshirsagar NA, Dalvi SS. Therapeuticdrug monitoring in a developing country: an overview. Br J Clin Pharmacol. 2001;52:103-8.

7. Forooghipour M, Mohammadpour AH, Mashhadian NV, Khayyat MH, Azarpajouh MR, Mokhber N, Aghebati T Shamsara J et al. TherapeuticDrugMonitoring of ValproicAcid in PatientswithMonotherapy at SteadyState. IranianJournal of Basic MedicalSciences.2009;12:146-9.

8. Patsalos PN, Spencer EP, Berry DJ. Ther apeutic drugmonitoring of antiepileptic drugs in epilepsy: A 2018 Update. Ther Drug Monit. 2018;40:526-48.

9. Aydın O, Ellidag HY, Eren E, Yilmaz N et al. Thelaboratoryshouldactively be involved in the therapeutic drugmonitoring (TDM) Process. IndianJournal of Pharmacy-Practice, Vol 9, Issue 1, Jan-Mar, 2016.

10. Nwobodo N. Therapeutic drug monitoring in a developingnation: a clinicalguide. JRSM Open. 2014;8:5.

11. Yamantürk P, Ozek M, Sevgi S, Eroglu L et al. Therapeutic drug monitoring in Turkey: experiences from Istanbul. Ther Drug Monit. 2000;22:545-8.

12. Cruz M. M, Ruiz M. E, Romero A. A. C, Robles-Piedras A. L et al. Appropriateness of Antiepileptic Drug-Level Monitoring at A Childrens' Hospital in Mexico. Biomedical&PharmacologyJournal. 2017;10:329-35.

13. Taur SR, Kulkarni NB, Gogtay NJ, Thatte UM et al. An audit of therapeutic drug monitoring services of anticonvulsants at a tertiarycare hospital in India. Ther DrugMonit. 2013;35:183-7.

14. Long PW. Phenytoin: Drugmonograph. In: Internet mentalhealth. [Online]1995-2008. [cited: 2019 Jan 11]. Availablefrom: URL: http://www.mentalhealth.com/drug/p30-d05.htm.

15. Adrian MB. Drug interactions that matter. The Pharmaceutical Journal 1999;262:325-7.

16. Aynacioglu AS, Brockmöller J, Bauer S, et al. Frequency of cytochrome P450 CYP2C9 variants in a Turkish population and functional relevance for phenytoin. Br J Clin Pharmacol. 2001;48:409–15.

17. Liao K, Liu Y, Ai CZ, Yu X, Li W et al. The association between CYP2C9/2C19 poly morphism sandpheny to inmaintenance doses in Asian epileptic patients: A system aticreview and meta-analysis. Int J Clin PharmacolTher. 2018;56:337-46.

18. St Louis EK. Monitoring antiepileptic drugs: a level-headedapproach. Curr Neuropharmacol. 2009;7:115-9