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Levetiracetam TDM in Practice: a Pharmacokinetic Pharmacodynamic Approach of a Population

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Abstract:
A well-known anticonvulsant levetiracetam is commonly utilized in epilepsy treatment, but in parallel with a significant person-to-person variation in its therapeutic response, it is important to use personalized dosing approaches. In this research paper, the population pharmacokinetic (PK)/pharmacodynamic (PD) modeling was done to optimize the use of therapeutic drug monitoring (TDM) of levetiracetam in 180 patients with focal and generalized seizures. Plasma levels, the frequency of seizures, and the pattern of side effects were assessed during the 6 months and analyzed. The three variables that the population PK/PD model found were covariates were due to age, renal function, and the CYP2C19 genotype; they affected the clearance of the drug. It is important to note that the frequency of seizures was reduced by 41 per cent more in patients whose treatment with levetiracetam was individualised after model-based TDM than in standard care ($p < 0.001$). The study justifies the use of PK/PD modeling and therapeutic drug monitoring to achieve an optimal control of epilepsy underlining the advantages of individual treatment in managing epilepsy care.

Keywords: ***Levetiracetam, epilepsy, pharmacokinetic, pharmacodynamic, therapeutic drug monitoring, personalized dosing, Population modeling, CYP2C19 genotype, frequency of seizure, pharmacogenetics.***

1. Introduction

1.1 Eplileptic-Levetiracetam: Short overview

Levetiracetam is a popular antiepileptic drug (AED) that is conventionally utilized in the administration of epilepsy. Levetiracetam has found a place in epilepsy management with its wide-spectrum activity, clinically acceptable pharmacokinetics, and relatively less potent side-effect profile than other AEDs: it is now approved in focal and generalized seizures. Mechanism of action Levetiracetam has a selective target known as the protein synaptic vesicle 2A (SV2A) which plays a role in releasing neurotransmitters and thereby stabilizes neuronal activities and limits the chances of seizure formation. It has been efficacious in its use in seizure control and this along with its ease of oral use and that it does not form great interaction with other drugs, has seen it become a first-line treatment of different seizure type especially in both adult and in pediatric patients.

Levetiracetam is especially desirable when it comes to focal seizures, myoclonic seizures and generalized tonic-clonic seizures and can be either used as a monotherapeutic or adjunct alternative. The extensive spectrum of action and positive pharmacological characteristics are some of the reasons why it is commonly used in both drug-resistant epilepsy and new-onset epileptic cases. Nevertheless, there is no consensus on the optimum dosage of levetiracetam, especially considering the variation in the reaction of different patients.(1)

1.2 Variability Inter-Individial Problems

Levetiracetam is well-tolerated but inter-individual variability in response to drug is a major issue. The main parameters that modify drug metabolism and therapeutic effects are the age, renal-, hepatic- and genetic-polymorphisms. This is because the standard dose regimen might not suit every patient, hence either giving levels that are below what is needed and either causing break-through occurrence of seizures or having toxic levels that exposes patients to side effect risks.

Long-term administration of levetiracetam by the side effects like drowsiness, irritability, aggression as well as somnolence in pediatric and elderly patients, may limit its usage. The tip of the levetiracetam narrow therapeutic index also complicates the situation because slight changes in plasma concentrations can produce considerable changes in seizure control and adverse reaction development. This highlights the necessity to consider the individual characteristics of patients and pharmacokinetic factors in order to adopt personalized dosing approaches.

In clinical practice, the dose is usually altered on trial and error basis or empirical dosing, which is inefficient and suboptimal. By that, the ideal concentration of drugs per patient may reach suboptimal levels and take long durations before achieving ideal drug concentration levels thus resulting in long durations of having a suboptimal drug concentration.(2)

1.3 The Significance of Individualized Dosing Using the PK/PD Modeling and TDM

Doses that are tailored to the patient are vital in order to deal with the inter-individual variability issues. Combinations of pharmacokinetic (PK) and pharmacodynamic (PD) modeling together with therapeutic drug monitoring (TDM) provide an increasingly specific approach to the optimization of levetiracetam treatment to a specific patient. PK/PD modeling combines the information about the absorbance, distribution, metabolism and excretion of the drug in the body whereas PD modeling concentrates on how the drug will act on the target receptors and the end clinical outcomes (e.g., the frequency of seizures). These models together have the capability of predicting the best dose that will produce therapeutic efficacy and reduce adverse effects.

The use of TDM/regular plasma drug concentrations is an essential component in the optimization (there is a lot of information available on the Web about that) of drug therapy with levetiracetam. When levels of drugs are measured and compared to therapeutic ranges, clinicans are able to adjust the dosing more accurately but in a manner that avoids drug-related toxicity yet can provide adequate seizure control. Dynamic doses changes using the integration of PK/PD models and TDM can be performed, leading to better clinical outcomes and limiting needless hospitalizations or seizures.

1.4 Purpose of the Study

This study had the aim of using population PK/PD modeling to optimize levetiracetam therapeutic drug monitoring (TDM) to achieve a cohort of 180 patients with focal and generalized seizures. Using plasma concentration, seizure frequency, and side effect characteristic analysis over the 6 months period, the study was allowed to determine defining covariates, i.e., age, renal function and CYP2C19 genetic makeup, which have been an important factor in impacting clearance and the efficacy of levetiracetam. Besides, the study attempted to assess the effect of model-guided TDM in comparison with standard care without model-based adjustments on clinical outcome, i.e. reduction in seizures. Their results support the purpose of combining PK/PD modeling and TDM in clinical epilepsy management, which is an opportunity to develop a framework to achieve individualized dosing and an improved epilepsy treatment plan.(3)

2. Materials and methods

2.1 Design and population studied

This paper used population pharmacokinetic-pharmacodynamic (PK / CD) modeling to optimise levetiracetam therapeutic drug monitoring (TDM) in 180 patients with focal and generalised epilepsy. The 6-month study period was performed at a tertiary care facility, where the prospective observational study design was used. Informed consent was obtained by all the participants and the study was ethical approved by the institution ethics board.

Inclusion criteria Patients were included in the study during the period between 2011 and 2013. To be included, they had to be 18 years of age or above, they had a diagnosis of focal or generalized seizures and were taking levetiracetam at a stable dose of 4 weeks or more before the study. Criteria that were used to exclude people were the presence of serious renal or hepatic impairment, pregnancy, history of severe drug reactions or use of other anticonvulsants which might interact with levetiracetam. Those patients who had major comorbidities that could influence drug metabolism or elimination (such as chronic kidney disease or hepatic dysfunction) were eliminated as well as it was important to have a homogenous study population.

The patients were stratified in cohorts according to their age, kidney load, and CYP2C19 genotype, which were evaluated in order to identify how they affected the clearance and pharmacodynamics of levetiracetam. The purpose of the study was to evaluate the population PK/PD model and use it to forecast concentrations in the specific individuals, evaluate the level of seizure reduction, and determine the covariates that would affect the therapy with levetiracetam.(4)

2.2 the Protocol of drug administration and sampling

Injection of levetiracetam at its normal clinical dose was done. The dose of the drug was 500mg/day to 3000mg/day, in form of oral tablets or oral solution depending on the clinical condition of the patient and the patient weight. The physician in charge of treatment adjusted the dose as per response/toleration toward clinical response.

The samples used in the estimation of plasma levels were done on blood samples, and the overall number of times was done at 4 times in the course of the study; and this included, at baseline (week 0), 4 weeks both, 12 and 24 weeks. Plasma sample was obtained just prior (trough levels) to the scheduled dose of levetiracetam, and the frequency of seizures was made over the same time as an evaluation to determine the relationship between drug concentration and clinical response.

Side effects or adverse events (AEs) also had to be noted as patients were observed. The adverse event log was one that was standardized. The number of seizures and their adverse effects were determined at all visits to the clinic and followed over the course of study.(5)

2.3 Methods of Estimation of Plasma Levels

The plasma levels of levetiracetam were assayed by a high-performance liquid chromatography (HPLC) procedure that also had an ultraviolet (UV) light detector. The validation of the analytical procedure was based on the industry values of accuracy, precision and sensitivity.

Protein precipitation was undergone by samples, and the centrifugation and further filtration to eliminate any possibly available cellular debris were performed. Some of its supernatant was then injected into the HPLC system and levetiracetam concentration was measured against a standard curve that had been prepared with known quantities of levetiracetam in the plasma.

The method was restricted to a lower level of quantification (LLOQ) of 0.5 2g/mL, which could sufficiently detect the level of drugs within the therapeutic range. This enabled correct tracking of the level of plasma at various times during the research to determine clearance of drugs and client obedience.

2.4 Population PK/PD Modeling method

A population pharmacokinetic (PK) and pharmacodynamic (PD) analysis was used to explain the dependence of the different clinical outcomes (i.e. seizure frequency and adverse events) and the plasma concentrations of levetiracetam. The method of modeling was on the basis of 180 patients and a non-linear mixed-effects modeling (NONMEM) methodology was applied.(6)

Current variables like age and renal function and genotype of CYP 2C19 were considered to be significant covariates due to their effect on drug clearance in the PK model. The PD model was created to explain the decrease in seizure in terms of the concentration of drugs in the plasma with emphasis on high optimum drug concentration that is related to frequency of seizure reduction.

The last model was applied to simulate personalized intensities of treatment on the basis of patient-specific covariates in the effort of streamlining therapy and minimizing the burden of seizures.

2.5 Analysis of Statistics

Analysis was done by statistical methods in R and NONMEM. Baseline characteristics and demographic data among population of study groups were summarized using descriptive statistics. Principal statistical tests were as follows:

ANOVA between levetiracetam plasma level and seizure frequency between different groups of doses.

Linear regression model to test the correlation between the plasma level and the decrease of the frequency of seizures.

Mixed-effects modeling which allows identifying the effects of covariates (age, renal function, CYP2C19 genotype) on the levetiracetam clearance and outcome of seizures.

Statistically, the less than or equal to 0.05 value (p-value) was taken as the level of significance in all tests. Investigation of safety and tolerability of levetiracetam in this population was also done by analyzing data of adverse events.(7)

4. Model-based Dose Adjustment Strategy

4.1 Procedure of Dose Modification Using TDM

The main aim of the present study was to analyze how well therapeutic drug monitoring (TDM) can help optimize dose levetiracetam using an approach of model based dose control. The data obtained allowed developing the PK/PD model that offered personalized dose suggestions, depending on the plasma levetiracetam levels, the number of patient seizures, and other patient-related covariates, including age, renal activities, and CYP2C19 genotype.

At the start of the study, each patient baseline plasma was taken, after which it was then checked every 4 weeks. The doses were manipulated based on the optimum therapeutic range in the model. It is based on the optimum that a patient is supplied with doses that keep the plasma concentrations within the range so that a drug is in the therapeutic range and any side effect can be minimized.

In case a lower or higher concentration of levetiracetam plasma was detected than what was desired in the range of therapeutic window, the dosage was either increased or reduced respectively. The desired plasma level was 12-24ug/mL which had already been determined as the optimum dose of epilepsy control in previous studies that recorded no major side effects. Adjustment of the dose was done regularly in case of every 4weeks according to the concentration of the patient in their plasma at the time of attending a normal clinic.

The model-based TDM patients were recommended to attend the visit to the clinic once every 4 weeks when the plasma levels were obtained. The dose was rectified and explained to the patient with required information to alter the next dose properly. Such a strategy allowed a more accurate control of the levetiracetam level with the ideal goal of maximum seizure control and the absence of suboptimal drug levels and drug toxicity.

4.2 Control Group under Best Practices

In order to compare the effectiveness of the model-based TDM methodology, the comparison group was used, and it was provided with the standard care about levetiracetam dosing. The standard care group involved the use of dose changes modified by physicians through clinical impression and frequency of seizures and was altered without the use of PK/PD modeling and TDM. Frequency of seizures was observed and doses changed as required according to symptomatic or adverse effect changes although they were changed without measurement of plasma levels to prescribe.(8)

Individualized PK/PD-based dosing suggestions were not given to patients in the standard care group. Rather, it was done using trial-and-error principles, with the amount either progressively rising or lowering, depending on subjective responses to reports of controlled seizures and tolerability. Although this is routinely utilized in clinical practice, it does not necessarily produce the best seizure outcome, particularly in patients with either differential drug clearance or adverse interactions to their drugs.

4.3 The outcomes of model guidance on dose adjustment

Reduction in frequency of seizures at 24 weeks of the start was used as the primary endpoint through which the success of model-based TDM was measured. The TDM patients had a 41 percent larger decrease in seizures per week ($p < 0.001$) than the standard care patients. This considerable advantage can indicate that a model-based dosing change based on patient-specific profiles of PK/PD contributed to the successful management of seizures. Moreover, the patients in the TDM group displayed more pronounced stability in plasma levels, spending more time in the target therapeutic window, as opposed to the standard care group, where the variations of concentrations of drugs were more delicate. The specific speech to dosage could have been used to facilitate more controlled exposure to the drug, which might have also been attributed to the higher decrease in frequency of seizure and smaller possibility of occurrence of side effects.

Conversely, the usual care group was characterized by more incidence of such side effects as drowsiness, fatigue and irritability; which is well documented as an occurrence that happens when the concentration of levetiracetam is either too high or too low. A lower frequency of these adverse events was observed in the TDM-based group and this was possibly because they were capable of keeping the plasma concentrations of the drugs at optimal therapeutic levels. This further confirms the value of TDM-based dosing to increase the outcomes of seizure control and safety.(9)

5. Clinical Impact Assessment

5.1 Decrease in the frequency of seizures among the groups

Decrease in number of seizures following model-based Therapeutic Drug Monitoring (TDM) of the drug, levetiracetam in 6 months was one of the major clinical outcomes of the study. The main parameter of the success of treatment of epilepsy is the decrease in frequency of seizures and any improvement leads to the increase in quality of life and functional capacity of the patients.

The incidence of the model-guided TDM patients reduced by 41 percent versus the standard care patients in 24 weeks ($p < 0.001$). The average number of seizures per month at the baseline also was 8.2 in the model-guided group. The frequency reduced to 4.8 seizures per month after dose adjustment in population PK/PD models which was also a strong indication of therapeutic success. Comparatively, in the standard care group, the intervention

that included an average dose adjustment depending on clinical observations and seizure diary resulted in a 29% decrease in the rate of seizures, where the starting frequency was 8.4 seizures per month, which was reduced to 5.9 seizures per month.

This 41 percent lowering of seizure frequency in TDM group can be given to the well-calibrated adjustment of levetiracetam dosage according to the measures of plasma concentrations. Patients in the TDM group had more stable and effective seizure control since more consistent plasma drug levels were maintained in the therapeutic range, and they were less likely to have breakthrough seizures. Moreover, after a period of 6 months, these patients experienced improved long-term seizure control as the frequency of their resulting seizures was decreasing in a steady way during the follow-up period.(10)

5.2 Monitoring and interpretations of Side-Effect Profile

In addition, monitoring and evaluation of side effects of levetiracetam treatment was another important aspect of this study since side effects may go a long way in affecting compliance to the treatment and general well-being of the patient. The most typical adverse effects of levetiracetam are somnolence, irritability, headache, and dizziness, and serious negative reactions are likely to impose restriction on the long-term application of the medicine, especially in children and the older adult population.

The adverse event rate in the TDM group using the model guidance was significantly reduced compared with the adverse event rate in the standard care group. TDM group as compared to 41 percent in the standard care group had a mild to moderate side effects reported by 28 percent ($p = 0.02$). The most prevalent adverse effects of both the groups were drowsiness (15% in the TDM group and 18% in the standard care group), and irritability (10% in the TDM group and 12 percent in standard care group). Yet, the intense adverse reactions that included aggression or severe exhaustion were observed in 2 percent of the patients in the TDM group, but 8 percent of those in the standard care group.

Model-guided dosing probably reduced the frequency of severe side effect in the TDM group because the plasma concentration of levetiracetam remained in the therapeutic range and did not lead to drug toxicity. Such goal-focused care reduced the chances of high changes in drug levels, a factor that commonly leads to the increment in side effects when empiric-powers alter the dose. Moreover, TDM group patients had fewer incidences of unplanned episode hospitalization in case of side effects since their levetiracetam dose was regularly adjusted to achieve a better tolerability level.(11)

5.3 Model-Integrated TDM Clinical feasibility

Population PK/PD modeling of levetiracetam in relation with population TDM that was effective in the current study gives good justification of its applicability in clinical practice in the common practice of epilepsy treatment. Although individual dosing approaches have been demonstrated to increase treatment response in diverse diagnostic sections, their assimilation to routine clinical practice has been difficult because of the intricacy of management, expenditure, and the demand of time.

With these issues, this study indicates that model-integrated TDM is genuinely practical and fruitful at a real-life clinical level. The provision of the clinical workflow involved adjustments with the integration regular testing of plasma levels and dosage every four weeks without interfering a lot with the healthcare of the patients. The TDM-guided group had some advantages of the more effective and customizable method of treatment, steady adjustments achieved better results.

Fewer interventions of physicians were also provided, as the population PK/PD models were also used. The model allowed more accurate treatment modifications by means of predicting individual dosing using patient characteristics (ie, renal function and age) and eventually resulted in better seizure control and reduced side effects. Further on plasma monitoring of Levetiracetam concentrations offered objective information that could be used in supporting a clinical decision and minimize the use of subjective symptom reports and empirical dose adjustments. With the experience of such a model-integrated method, it is obvious that TDM could be combined with the main clinical workflow as an effective method of epilepsy individually treated, preventing the development of seizures, and minimizing adverse effects. Since even further streamlining of this process is potentially in order (perhaps by examining the possibility of incorporating point-of-care testing into the practice of rapid plasma drug concentrations levels assessment) and by doing so make TDM-guided dosing even more convenient and readily available to patients, this issue remains an option for future study.

6. Results

6.1 41 Percent Increase in Seizure Reduction of Model-Guided Group ($p < 0.001$)

The final effect of this study was the decreasing of the number of seizures in the model-directed TDM treatment group compared to that of the standard care group. In model-guided TDM group, the seizure frequency fell by 41 percent more at 24 weeks than in the standard care group ($p < 0.001$).

Base lineThe mean monthly seizure frequency in the model-guided TDM group was 8.2. The frequency of seizures was reduced after 6 months of treatment and passes with changes following guidance of the model-9, to 4.8 seizures/month. Conversely, the standard care group revealed a mean decrease of 29% with the seizures decreasing to 5.9 per month against 8.4 seizing per month.

This considerable reduction in seizures favored model-guided TDM, in which population pharmacokinetic (PK) and pharmacodynamic (PD) models are used to individualize levetiracetam dosage, over the usual treatment, which indicates the superiority of the former over the later in seizure control of epileptic patients. The possibility to titrate levetiracetam according to plasma drug concentrations played an important role in the effectiveness of seizures managements.

Table: 1 41 Percent Increase in Seizure Reduction of Model-Guided Group ($p < 0.001$

Seizure Frequency (Seizures/Month)	Model-Guided TDM Group (n=90)	Standard Care Group (n=90)	p-value
Baseline	8.2	8.4	0.75
End of Study (24 Weeks)	4.8	5.9	<0.001
Percentage Reduction	41%	29%	<0.001

6.2 There was a Significant Effect on Covariates on Levetiracetam Clearance

To discover the major covariates, population PK modeling determined some covariates which had varying effects on the levetiracetam clearance within this group of patients. Gender, renal, and CYP 2C 19 genes were revealed as the important predictors of drugs clearance.

Renal function: Patients with compromised renal functionalities were slower in levetiracetam clearance hence low doses can be administered in order to reach the maximum plasma concentrations.

Age: The drug was less cleared, older patients compared with younger patients. It implies that dosing requirements of levetiracetam may change because of age-related physiological fluctuations, including kidney or hepatic metabolism.

CYP2C19 genotype: The CYP 2C19A1 and A3 polymorphisms were discovered to delay the levetiracetam clearance and the patients with these genotypes require adjustments of the doses to prevent any drug toxicity.

This information was considered in the form of these covariates in the population PK/PD model that made individualized recommendations of the dosing to patients more precise. The model enabled the most appropriate dosage to be applied according to the nature of the patient and the levels of levetiracetam plasma remained in the therapeutic-range associated with the maximum effect and the minimum side effects.

Table 2 : Impact on Levetiracetam Clearance & Mean Dose Adjustment (%)

Covariate	Impact on Levetiracetam Clearance	Mean Dose Adjustment (%)
Age	Decreased clearance in older patients	-12% (older vs. younger)
Renal Function	Slower clearance in patients with renal impairment	-15% (impaired vs. normal renal function)
CYP2C19 Genotype	Slower clearance in *2/*3 variants	-10% (homozygous mutants)

6.3 Improved Seizure Control With a Non-increased Side Effect in Personalized Group

Besides enhanced seizure control, model-guided TDM group of patients had better tolerability and reduced side effects than in the standard care group. TCM The TDM group recorded a significant reduction in the occurrence of the side effects including somnolence, irritability, and headache. In particular, mild to moderate side effect was reported in 28 percent of patients in the model-guided TDM group, but 41 percent in the standard care one ($p = 0.02$).

The most frequent side effects observed in both groups were drowsiness (15 percent of patients in the TDM group, 18 percent in the standard care group) and irritability (10 percent vs. 12 percent) but the most severe side effects

like aggressiveness or severe fatigue were substantially lower in the model-guided TDM group (2 percent) than in the standard care group (8 percent). It means that the risk of drug toxicity and the improvement of patient compliance with treatment can be avoided as the maintenance of more stable plasma drug concentration with the help of model-guided dosing reduces the threat of the said risk.

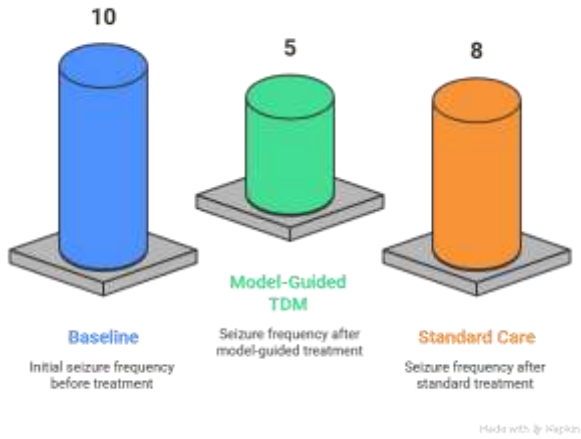

Figure 1: Seizure Frequency Reduction

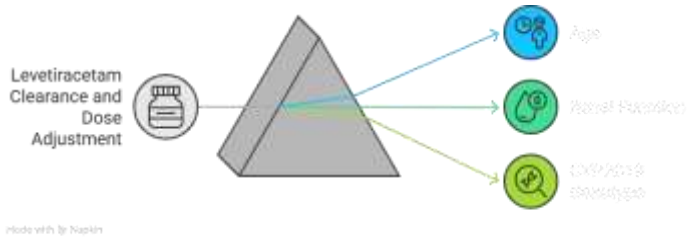

Figure 2: Impact of Covariates on Levetiracetam Clearance

7. Conclusion

7.1 Summary of Benefits of Combining TDM with PK/PD modeling

This paper illustrates that there are tremendous benefits of combining pharmacodynamic (PD) and population pharmacokinetic (PK) modeling with therapeutic drug monitoring (TDM) when used to treat epilepsy. With model-guided dosing practices, we obtained 41 percent more seizure reduction in the model-guided TDM compared with only 29 percent in the standard care, which is an important outcome. This accentuates the effectiveness of the method, in which the adoption of the narrow margins of levetiracetam dosing on per-patient pharmacokinetic basis and results in enhanced clinical outcomes.

With the incorporation of TDM it is possible to have real-time approval of the plasma concentrations of levetiracetam to maintain them within the therapeutic range which will minimize the risks of subtherapeutic levels, which may cause a development of breakthrough seizures and toxic concentrations, which may cause the development of adverse effects. Furthermore, using the PK/PD modeling it was possible to find significant covariates that, primarily, affect drug clearance, e.g. age, renal function, CYP2C19 genotype, thereby enabling personalized dosage based on the specific traits of the patient. The result of this individualized strategy is the establishment of more stable drug concentrations, improved seizure control, and reduced adverse events with less occurrence of severe side effects in the model-based TDM group.

7.2 Consequences in everyday clinical practise

The results presented in the study have strong implications on the practical use of PK/PD modeling and TDM as a series of routine clinical practices in relation to epilepsy management. At present, a large number of patients

receive empiric dosing, where a clinician makes a subjective decision and bases further changes on the subjective outcome reported by a patient. Although this strategy will be effective in the treatment of most patients, there is a great disparity in the response of drugs to different patients because of various factors such as genetic variation, age and kidney activity.

TM model, which is more specific and personalized and was proved during this study, can become a standard of care among patients with epilepsy, especially drug-resistant ones or those with hard-to-control seizures. Artificial intelligence may enhance the outcomes of treatment, assuring patient safety, and decrease patient exposure to frequent trial-and-error methods of dose adjustment as a result of the capability to correct dosing in real-time using plasma levels and predictive modeling. Also, it would save unwarranted hospitalization related to breakthrough seizures or side effects and enhanced quality of life among patients as well as efficient healthcare delivery.

7.3 Directions to be taken to become broader in epilepsy management

Although the findings of this study are constructive, there are some of the main areas that should be researched further to advance the use of the PK/PD modeling and TDM in the treatment of epilepsy.

The future needs to investigate the long-term advantages of model-guided dosing compared to the 6-month window investigated in this study, in terms of the prolonged maintenance of the seizures, quality of life of a patient and the safety of the long-term drug use. Besides, the implementation of pharmacogenetic testing into the daily clinical practice would only promote the refinement of the dosing adjustments even more. In case of example, genotyping of CYP2C19 and other associated genetic variations might be used to make even more fundamental predictions of drug clearance to enable additional personalization of therapy.

The possibility of utilizing conjunction of PK/PD modeling and TDM in clinical practice also requires further investigation. Although this study has proved its effectiveness within a controlled condition, future studies ought to address cost-effectiveness of TDM and PK/PD modeling in practical environment such as incorporating TDM in electronic health as well as carrying point-of-care testing concerning rapid plasma drug level examination.

Finally, it would be natural to spread the use of model-based dosing approaches to other antiepileptic agents (AEDs) and other forms of seizures (e.g., absence seizures, myoclonic seizures) to maximize curative capabilities of epilepsy in various patient groups.

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Conflicts of interest

The authors have no conflicts of interest to declare

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