Research Article

Design of drug dosage regimen for valproate: Exploring modeling and simulation based approach

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ABSTRACT

Background: Population pharmacokinetic studies attempt to explain the variability in pharmacokinetics among study subjects and explore the role of covariates on the pharmacokinetics. The present study was planned to evaluate by simulation, the various dosage regimens of valproate and their predicted relevance to achieve desired therapeutic ranges and to see the effect of various covariates.

Materials and Methods: This study utilized the previous database of therapeutic drug monitoring data of valproate available in the department and population pharmacokinetic models developed by a group in the department. From the database, 93 patients' details have been used in this study. The simulation studies were carried out for various dosage regimens such as 400mgQ12Hr, 500mgQ12Hr, 800mgQ12Hr, 1000mgQ24Hr for 100 simulated patients using NONMEM software package.

Results: 500mg BID dosage regimen was found to be more advantageous as more number of simulated patients were having the C_{ss} within the therapeutic range and the effect of covariates like sex and concomitant phenytoin use were found to be insignificant but with 1000mg OD regimen in females, the number of individuals with C_{ss} within the therapeutic range were found to be less with which we could say that the induction effect of phenytoin on valproate metabolism in females could be more than that of males.

Conclusion: The present study was able to predict steady state concentrations for various dosage regimen scenarios with possible pharmacokinetic and therapeutic outcomes. This study underscores the relevance of population pharmacokinetic based simulations in dosage regimen design.

Key words: Population pharmacokinetics, Simulations, valproate, dosage regimen, NONMEM.

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INTRODUCTION

Population pharmacokinetics (PoPK) has been defined as the study of the variability in plasma drug concentrations between individuals when standard dosage regimens are administered.[1] Dose concentration relationship can be altered by patient demographics, pathophysiology, and therapeutic features, such as body weight, excretory and metabolic functions, and the presence of other therapies. So, to design the dosage regimen appropriately there is a need for conducting population pharmacokinetic studies.[2]

PopPK approach has an application in the exploratory and confirmatory stages of drug development by explaining the quantitative relationships among drug regimen, patient characteristics, and drug disposition. The nonlinear mixed-effects modelling approach is especially helpful in certain adaptive study designs, such

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as dose-ranging studies (e.g., so called titration, or effect controlled designs). It also has application in patient care by providing quantitative and semi-quantitative guidelines for individualization of drug therapy.[3]

Simulation is the process which involves in building a mathematical model that mimics a real world situation and then using the same model to conduct experiments to investigate and predict the behaviour of that situation.[4]

Pharmacokinetics simulations are explored and attempted in rational designing of dosage regimen in number of clinical situations. Many a times simulations are used to study the effect of various dosage regimen and the impact of various patient covariates on the resultant pharmacokinetic and pharmacodynamic parameters.[5-9]

The main aim of this study was to analyze the existing data base on valproate collected for previous therapeutic drug monitoring studies in the pharmacy practice department using NONMEM package to develop simulations for dosage regimen and to interpret the simulation outputs based on steady state concentration. This will enable to make decisions on dose selection based on the median measures of drug concentrations and number of patients who fall within, below and above therapeutic range.

MATERIALS AND METHODS

Patients and tools

Ethical approval was taken from Institutional ethics committee of Kasturba Hospital, Manipal The present study was planned to use the existing therapeutic drug monitoring data base of valproate in the department of Pharmacy Practice and develop simulations to optimize the dosage regimen. A population pharmacokinetic model for valproate has been already developed by Mallayasamy et.al.[10] Using the same model simulations were performed for different dosage regimens employing NONMEM software package (Version 7.2) by using a front-end application Pirana (version 2.5.0). The simulation outputs were generated using the 'R' Package (2.15.0) and analyzed.

Simulation Method

Demographic data, pharmacokinetic data and covariates of the pre-existing model were used for the current simulations. Dosage regimens simulated were 500mg BID, 1000 mg OD, 400mg BID and 800mg BID, each with 100 hypothetical subjects. Control streams were written for performing simulations with and without covariates (sex and phenytoin use in clinically useful dose). Data files were created for different dosage regimens with different combinations of sex and phenytoin use for 100 patients. Simulations were performed using NONMEM with '$SIM' option. The plasma drug concentrations at steady state were simulated and their median concentrations were calculated. Percentages of patients falling within and outside the therapeutic range for each dosage regimen were estimated.

RESULTS

For the current study various dosage regimens normally used in the routine practice for the management of seizures were used for simulations. Totally four doses 400 mg, 500 mg, 800 mg and 1000 mg were used for simulations. Sex of the patient and use of phenytoin was considered as covariates for the present simulations. Each dosage regimen had 5 conditions for simulations resulting in a total of 20 different simulations. (Table.1)

When the data of the simulation studies are evaluated for the pattern of median concentrations resulting from various dosage regimens, pharmacokinetic outcomes could be predicted. The results of the study showed that 500mg BID dosage regimen had maximum patients within therapeutic range i.e, 50-125mcg/mL compared to other dosage regimens. 800 mg BID regimen group had more than 50% patients above the therapeutic range whereas the 400 mg BID had around 35% patients below

Table 1: Various dosage regimens used for simulations

Simulation Number	Dosage regimen	Description
1	400 mg BID	Without covariates
2	400mg BID	Males and phenytoin use
3	400mg BID	Males and without phenytoin
4	400mg BID	Females and without phenytoin
5	400mg BID	Females and with phenytoin
6	500mg BID	Without covariates
7	500mg BID	Males and phenytoin use
8	500mg BID	Males and without phenytoin
9	500mg BID	Females and without phenytoin
10	500mg BID	Females and with phenytoin
11	800mg BID	Without covariates
12	800mg BID	Males and phenytoin use
13	800mg BID	Males and without phenytoin
14	800mg BID	Females and without phenytoin
15	800mg BID	Females and with phenytoin
16	1000mg OD	Without covariates
17	1000mg OD	Males and phenytoin use
18	1000mg OD	Males and without phenytoin
19	1000mg OD	Females and without phenytoin
20	1000mg OD	Females and with phenytoin

the therapeutic range. Patient group on 1000mg OD had lower median concentrations than 500 mg BD concentrations (Table 2 & Fig.1- 4). There was no difference in the effect of covariates among the various simulated conditions for each dosage regimen. Where as in the case of 1000 mg OD in female patients with phenytoin, there is a large decrease in the number of patients (46%) within the therapeutic range compared to other groups (Table 3).

DISCUSSION

Present study was planned to take advantage of the available therapeutic drug monitoring data and population pharmacokinetic model to develop simulations on dosage regimen. In the late 70s and 80s Sheiner and colleagues published on new approach of pharmacokinetic analysis known as population pharmacokinetics. They published on population pharmacokinetics of phenytoin from the data collected from therapeutic drug monitoring of patients taking this drug. This approach was shown superior to naïve pooling of data and

Table 2: Dosage regimen and concentration ranges of valproate

Dosage Regimen	Median concentrations (Range in mcg/mL)	Above the range % (No.)	In range % (No.)	Below the range % (No.)
400mg BID	62.638 (5.73 - 156.01)	7% (7)	57% (57)	36% (36)
500 mg BID	78.29 (7.16 - 195.02)	16% (16)	60% (60)	24% (24)
800mg BID	125.27 (7.16 - 195.02)	51% (51)	42% (42)	7% (7)
1000 mg OD	72.133 (1.49 - 215.88)	17% (17)	52% (52)	31% (31)

OD – Once daily, BID – Twice daily

Table 3: Simulation of 1000mg Q24Hr Dosage regimen

Dosage Regimen	Simulation	Avg	SD	Median (Range)	Above the range	In range	Below the range
1000mg	Normal	79.561	47.84	72.133 (1.4984 - 215.88)	17% (17)	52% (52)	31% (31)
OD	s1p1	77.48	42.133	74.68 (1.4984 - 215.88)	16% (16)	57% (57)	27% (27)
	s1p0	77.487	42.138	74.68 (1.4984 - 215.88)	16% (16)	57% (57)	27% (27)
	s0p1	74.281	48.89	64.47 (1.4984 - 215.88)	17% (17)	46% (46)	37% (37)
	s0p0	77.487	42.138	74.68 (1.4984 - 215.88)	16% (16)	57% (57)	27% (27)

S1p1-Male patients with phenytoin, s1p0-Male patients without phenytoin,
s0p1-Female patients with phenytoin, s0p0-Female patients without phenytoin

Figure: Simulated plasma concentrations of various dosage regimen

Figure 1: Simulation of 400mg BID

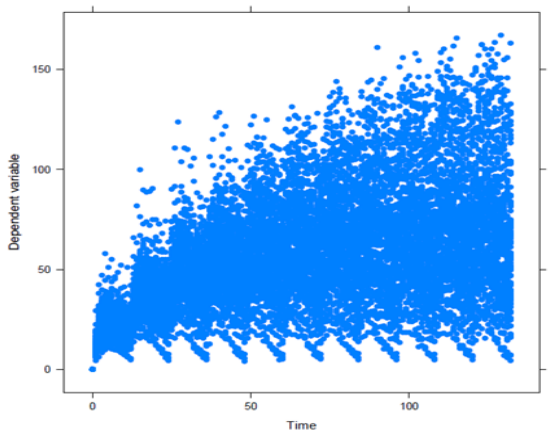


Fig.2. Simulation of 500mg BID

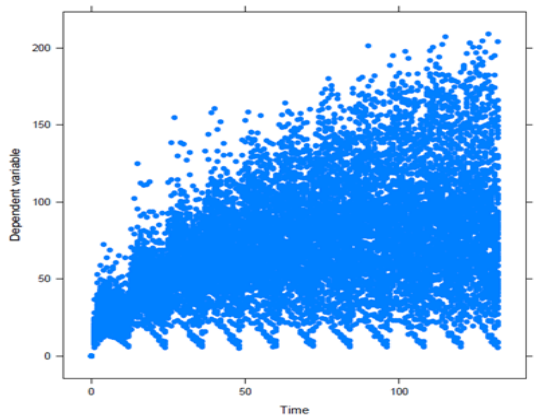


Fig. 3 Simulation of 800mg BID

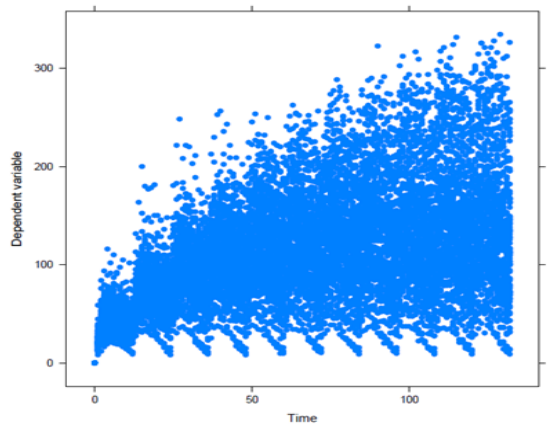
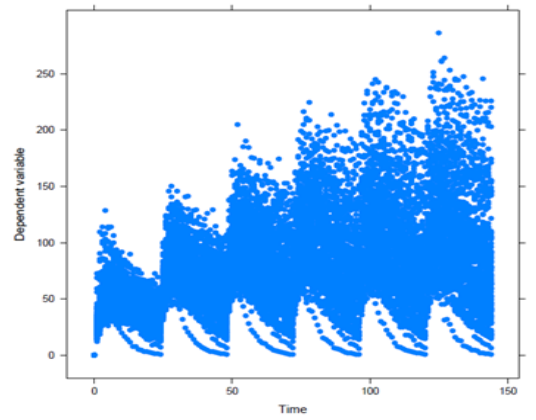


Fig 4. Simulation of 1000mg OD



two-stage approach.[11]

Number of population pharmacokinetic studies were reported for valproate using NONMEM. These studies reported population parameters like clearance, volume of distribution and absorption rate constant and their variance.[12-16] The population pharmacokinetic parameters used for the present study were taken from the work of Mallayasamy et al.[10] The values of pharmacokinetic parameters for the simulations were fixed to these values as this study was intended to simulate typical Indian patient. Reports are available on simulation studies of valproate.[17] Reported simulation studies assumed conditions like missed doses and dosing at different time points and the resultant concentrations. Reported studies tested various dosage regimens like 500 mg BID and as well as 1000 mg BID.[18] Present study also used these dosage regimens along with various other regimens used in the present setting for developing simulations.

Usually steady state trough concentrations are used for therapeutic drug monitoring studies as the trough concentrations are more stable compared to the peak concentrations which are subjected to high inter-patient variability.[19] In the present study the dosing scenario was predicted till 8 half-lives as the steady state can only be attained with 5 to 7 half-lives. Steady state median concentrations were used to interpret the results of simulations.

Patient group on 1000mg OD had lower median concentrations than 500 mg BD concentrations. In a study by Ahmed et al they also had similar observation of attaining higher median concentrations with 500 mg BID compared to 1000 mg OD regimen.[18]

Even though the percentage difference was lower between 400mg BID and 500mg BID groups, the median concentration was closed to the lower end of therapeutic range in 400mg BID group, so the 500 mg BID can be considered as optimal. The present study represents a population of adult age group and these simulations did not consider pediatric age group as the parameters were derived from adult population and used in this simulation. The current study simulated mean steady state concentrations with variability components from previous population pharmacokinetic data. Based on the inputs the variability observed in the concentration range was wider and this shows the role of monitoring and dosage adjustment.

The simulation study predicted potential scenarios with various dosage regimens and the potential therapeutic failure or success with each regimen. These simulations might be useful in clinical decision making or as an initial guide for dosage regimen decision. Population pharmacokinetics will help in assessing pharmacokinetic parameters in specific population. This approach can be implemented in our country as our population is diverse and pharmacokinetics might be different from the reported western literature. Population pharmacokinetic values derived from Indian population will help to simulate appropriate dosage regimens for various drugs and the present study precisely attempted that. One limitation for the present study is the size of simulations which is for 100 patients. Usually simulations will be performed with larger number of patients for better prediction and the present study could not do this because of lack of accessibility to high power computing facilities.

The present study was planned to simulate the outcomes of various dosage regimen scenarios and covariates on valproate concentrations. The dosage regimen with 500 mg BID was found to be optimal whereas other dosage regimens tested resulted in toxic range or subtherapeutic range in large proportion of simulated patients. Tested covariates did not have impact on the steady state concentrations except in the female group of 1000 mg group. Results of this study helps to decide empirical starting dose based on the desired steady state trough concentrations. This study underscores the relevance of population pharmacokinetic based simulations in dosage regimen designing.

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Not reported.

REFERENCES

1. Aarons L. Population Pharmacokinetics: Theory and Practice. Br J Clin pharmacol 1991; 32: 669-70.
2. Guidance for Industry population pharmacokinetics U.S. Department of Health and Human Services Food and drug administration. February 1999. Available at: www.fda.gov/downloads/Science research/ Special topics/ Womens Health research/ UCM133184.pdf accessed on 1|12|2012
3. Sheiner LB , Steimer JL. Pharmacokinetic/ Pharmacodynamic Modelling in Drug Development**.** Annual Review of Pharmacology and Toxicology.2000; 40: 67-95.
4. Holford NHG, Kimko HC, Monteleone JPR, Peck CC. Simulation of clinical trials. Annu Rev Pharmacol Toxicol 2000; 40: 209-34.
5. Katsube T, Yano Y, Wajima T, Yamano Y, Takano M. Pharmacokinetic/ pharmacodynamic modeling and simulation to determine effective dosage regimens for doripenem. J Pharm Sci. 2010; 99:2483-91.
6. Holly H.C. Kimko, Donna Skee, Joseph Massarella, IolandaCirillo. Modeling & Simulation Exercise to Recommend Dosage Regimens for Patients with End□Stage Renal Disease Receiving Haemodialysis.. Abstract presented at Population Approach Group in Europe Conference 2010;19:1775.
7. Guidi M, Arab-Alameddine M, Rotger M, Aouri M, Telenti A, Decosterd LA et al. Dosage optimization of treatments using population pharmacokinetic modeling and simulation. Chimia Inter J Chem 2012; 66:291-95.

8. Mould DR and Upton RN. Basic Concepts in Population Modelling, Simulation, and Model-Based Drug Development .CPT Pharmacometrics & Sys Pharmacol 2012;2:e38.
9. Tsuji BT, Okusanya OO, Bulitta JB, Forrest A, Bhavnani SM, Fernandez PB, Ambrose PG. Application of pharmacokinetic-pharmacodynamic modeling and the justification of a novel fusidic acid dosing regimen: raising Lazarus from the dead. Clin Infect Dis. 2011; 52 :513-19.
10. Mallayasamy S. Population pharmacokinetic study of lamotrigine and valproate in Indian epileptic patients [Dissertation].Manipal: Manipal University; 2011.
11. Bonate PL. Recommended Reading in Population Pharmacokinetic Pharmacodynamics. The AAPS J.2005; 7: 363-73.
12. Blanco-Serrano B, Oteroa MJ, Satos-Buelga D, Garcia-Sanchezt MJ, Serranoa J and Dominguez-Gill A. Population estimation of valproic acid clearance in adult patients using routine clinical pharmacokinetic data. Biopharm Drug Dispos.1999; 20: 233- 40.
13. Botha JH, Gray AL & Miller RA. Model for estimating individualized valproate clearance values in children. J Clin Pharmacol. 1995; 35: 1020-24.
14. Desoky EE, FuseauE ,Amry SE , Cosson V. Pharmacokinetic modelling of valproic acid from routine clinical data in Egyptian epileptic patients. Eur J Clin Pharmacol 2004; 59: 783-90.
15. Park HM, Kang SS, Lee YB, Shin DJ, Kirrit ON, Leek and YimDS.Population pharmacokinetics of intravenous valproic acid in Korean patients. J ClinPharmTher 2002; 27: 419-25.
16. Sanchez-Alcaraz A, Quintana MB, Lopez E & Rodriguez I. Valproic acid clearance in children with epilepsy. J Clin Pharm Ther 1998; 23: 31-34.
17. Ronald R C, Sandeep D. Does it really matter when a blood sample for valproic acid is taken following once daily administration of divalproex-ER? Ther Drug Monit.2006; 28:413-18.
18. Alaa AM, Douglas BF, William BH, Ronald RC, William GR. The use of Monte carlo simulations to study the effect of poor compliance on the steady state concentrations of valproic acid following administration of enteric coated and extended release –Divalproex sodium formulations. Biopharm Drug Dispos.2005; 26:417-25.
19. Ronald RC, Sandeep D. Predicted Serum Valproic acid Concentration in patients missing and replacing a dose of Extended Release-Divalproex Sodium. Am J Health-Syst Pharm.2004; 61:2284-88.

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