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ORIGINAL RESEARCH ARTICLE

Equivalence of the Steady State Concentrations of Two Dosage Regimen of Phenytoin Using Computer Optimisation Programme OPT6

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ABSTRACT

OPT 6 is an optimisation programme through which optimisation of various drugs like phenytoin can be done. It is based on Bayesian Statistical Theory and Maximum Likelihood Estimation. This study was aimed to determine the steady state concentration equivalence using the Optimisation programme OPT 6 to compare 300mg once daily phenytoin and 100mg tid phenytoin. Epileptic outpatients attending neurology department, were included. Twenty-four patients were enrolled into the study. Informed consent was taken. Liver and renal function was checked. Basal phenytoin levels were also estimated. Once preliminary tests were found to be normal the patients were randomised into one of the two treatment arms either 300mg once daily or 100mg thrice daily. Each arm was for a 2 week period. Peak and trough phenytoin concentrations were estimated. These results were entered into the optimisation programme along with demographic data for both regimens separately. Then the predicted steady state concentration was noted. Wilcoxon's Signed Rank test was done to find the difference in the predicted steady state concentration. There was no significant difference between steady state concentration (Css) using trough values of both dosing regimens. There was significant difference between Css using trough and peak values for both dosing regimens. There was no significant difference between Css using peak values of both regimens. This study has illustrated trough value can be used for dose adjustment of patients on phenytoin once daily and thrice daily using OPT6 programme.

Key words: phenytoin, steady state concentration, Progaramme OPT6.

INTRODUCTION

Phenytoin is one of the most commonly prescribed anti epileptic medications among physicians in India. Depending upon the patients' age, weight and disease severity, phenytoin has been prescribed at various dosages. There are several ways for the individualisation of drug dosage such as considering weight, creatinine clearance in case of renal failure or by using therapeutic drug monitoring. One of the methods is individualising the drug dosage using computer Optimisation programme. There are now a number of programs for dosage optimisation which run on IBM compatible, cirrus or BBC computers. They may be useful particularly when complicated drug regimens have been used and Bayesian feedback required. They cover a variety of drugs and some will allow other types of pharmacokinetic analysis to be performed. OPT 6 is an Optimisation Programme by which optimisation of dosage can be done for phenytoin, carbamazepine, theophylline, lithium, vancomycin, gentamycin and digoxin. It is a series of computer programs designed to assist dose optimisation for individual patients.It is based on Bayesian Statistical Theory and Maximum Likelihood Estimation [1]. OPT uses prior information on the distribution of population pharmacokinetic parameters and plasma drug concentration measurements to obtain the 'most likely' set of parameters for the individual.Using this programme complex dosage regimes and non-steady state conditions can be handled. OPT is designed for use in a Clinical Pharmacokinetics Laboratory where informed interpretation of results is essential.The drugs for which the system is currently available include theophylline, digoxin, lignocaine, disopyramide, gentamicin and phenytoin (steady state data only) [2].

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OPT6 is one of the programs most widely used and verified in UK .The information entered into the programme is used via equations based on Baye's theorem and the principles of maximum likelihood to estimate most likely set of pharmacokinetic parameters for that individual, i.e. clearance, volume of distribution, absorption rate constant where appropriate and the concentration at the start of present dosage history. This programme is meant for once daily regimen which uses trough value of phenytoin for dose adjustment. This study was aimed to determine the predicted steady state concentration using trough and peak values of both regimens. So that trough value of thrice daily regimen and peak value of once daily and thrice daily regimens also can be used for dose adjustment of phenytoin.

MATERIALS AND METHODS:

Study design:

A randomized double blind crossover interventional study

Methodology:

Ethical and Research Committee clearance was obtained. Following which trough and peak values were taken from the 22 patients who had participated in the phenytoin dosing study [3]. Patients were taking either phenytoin 100 mg thrice daily for 14 days or 300 mg once daily for 14 days.

A double blind protocol was followed throughout the study. Patients were asked to report to the hospital at the end of the two-week treatment arms. During that time, the compliance cards given to them beforehand were checked. Once full compliance of the prescribed regimen was assured, trough and peak serum concentrations of Phenytoin were measured.

Timing of the Blood Samples:

For the trough level– 7 ml of blood was taken at 8 AM before taking the morning dose of phenytoin

For the peak level– 7 ml of blood was taken 4 hrs after the morning dose

Totally 24 patients were enrolled into the study. Of which one patient developed nystagmus during once daily regimen and withdrawn from the study. Another patient was lost to follow up. So the trough and peak values of phenytoin from 22 patients were entered into the optimisation programme along with demographic data for both once daily and thrice daily regimen separately. Then predicted steady state concentration was noted.

First demographic data of each patient age, sex, height, weight, alcoholic status, whether smoker or not, serum creatinine levels, whether cirrhotic or not, any systemic illness, any other comedication and acetylator status if known were entered into the programme. Secondly the daily dosage and the trough value of the once daily regimen were entered into the programme. This data was optimised to get the dosage for a steady state concentration of 12μg/ml. Then nearest possible dose was entered. The programme predicted steady state concentration for that particular dose.

The peak value for the once daily regimen and was entered and the above process was repeated. The steady state concentration was again predicted.

In the same way steady state concentration was predicted by using trough and peak values of the three times daily regime separately.

Procedure for measuring drug levels in plasma:

Concentration was measured by the method of Dill[4]. Serum specimens were collected and kept frozen until analysis. High and low quality controls were stored alongside the patient specimen. This ensured that standards, quality controls and specimens were kept under the same conditions.

The statistical analysis:

Since the data were pair matched, Wilcoxon signed rank test was done to find the difference in the predicted steady state concentration of the following for the same dose.

a. Using trough values of two dose regimens
b. Using peak values of dose regimens
c. Using trough and peak values of once daily regimen
d. Using trough and peak values of three times daily regimen

RESULTS AND DISCUSSION

In this study there was no significant difference between the predicted steady state concentration (Css) using trough values of both dosing regimens shown in (**Table 1**). This indicates that dose adjustment can be done for three times daily dose of phenytoin using trough values also, provided the patient take the tablets at eight hours intervals.

There is significant difference between the predicted Css by using trough and peak values of once daily regimen shown in (**Table 2**). This explains that peak value cannot be used for

optimising the dose using once daily dosing of phenytoin.

There is significant difference between the predicted Css by using trough and peak values of thrice daily regimen (Refer Table 2). This also express that peak value cannot be used for optimising the dose using thrice daily dosing of phenytoin.

There is no significant difference between the predicted Css using peak values of both dosing regimen (Refer Table 2). Since there is significant difference using trough and peak values for both regimens this cannot be taken into consideration.

The Bayesian approach in pharmacokinetics involves the prediction of pharmacokinetic values, dosage regimens, and serum concentrations for drugs. Beginning with mean population pharmacokinetic parameters, one uses observed serum concentrations in individual patients to modify these parameters through Bayesian analysis to improve the accuracy of future serum concentration predictions [5]. So OPT6 programme also uses this basic principle for dose adjustment in phenytoin therapy. OPT [6,7] which estimates the most likely set of pharmacokinetic parameters for an individual patient using a relatively simple pharmacokinetic model and patient specific data such as age, weight, sex etc. This approach was originally proposed by Sheiner *et al*. [8], and by Peck *et al* [9]. Its success in practice when applied to digoxin and phenytoin has been demonstrated by Sheiner *et al* [10] and by Vozeh *et al* [11].

This study has illustrated that trough value of thrice daily regimen also can be used for dose adjustment of patients on phenytoin. Peak value cannot be used for dose adjustment of phenytoin by once daily and three times daily regimens. The OPT6 programme would be helpful for dose adjustment of phenytoin once daily and three times daily regimens. This should decrease the toxicity and improve seizure control with phenytoin. It is hoped that the findings of this study will help in overall management of epileptic patients in India.

Table 1: Mean (SD) of predicted steady state concentration (Css)

	Mean(SD) predicted steady state concentration	
Level (μg/ml)	A (300mg once daily)	B (100mg tid)
Using Trough values	11.74(0.79)	11.79(2.23)
Using Peak values	14.63(2.03)	13.82(2.44)

Table 2: P value using Wilcoxon Signed Rank test

Variables	P value *using Wilcoxon's Signed Rank test.*
Using trough values of both dosage regimens	0.907
Using peak values of both dosage regimens	0.119
Using trough and peak values of once daily regimen	0.0000
Using trough and peak value of thrice daily regimen	0.009

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