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Original Article

Pharmacology Section

A Prospective, Double-blinded, Crossover Study to Determine the Equivalence of the Serum Levels and the Peak Level Toxicity of Diphenylhydantoin (EptoinR)

S. BHUVANESHWARI, SUJITH CHANDY, SUDHIR KUMAR

ABSTRACT

Context: In India, phenytoin is often prescribed as twice daily or thrice daily dosage schedules. In the West, this practice has been changed to a once daily regimen in most of the cases. Can we in India follow suit? Is our physical and genetic make up with regards to the phenytoin pharmacokinetics different? Does this necessitate a multiple dosing regimen to avoid adverse effects or even breakthrough seizures?

Aims: This study was aimed at comparing 300mg once daily of phenytoin and 100mg tid of phenytoin in terms of its adverse effects, peak and trough serum concentrations.

Settings and Design: Out patients attending the Neurology Department, Christian Medical College, Vellore, India. This was a prospective, randomized, double blinded, crossover study.

Methods and Materials: Twenty-four patients were enrolled into the study. An informed consent was taken from them. Their liver and renal functions were checked. Their basal phenytoin levels were also estimated. Once the preliminary tests were found to be normal, the patients were inducted randomly into one of the two treatment arms, either 300mg once daily or 100mg thrice daily. Each arm was given for a 2 week period. Adverse effects were looked for and the peak and trough phenytoin concentrations were estimated.

Statistical Analysis Used: The mean, SD and the P values were obtained by the Per Protocol and the ITT (Intention to Treat) analysis of the trough and peak serum levels by using Wilcoxon's signed rank test.

Results: One patient experienced an adverse effect in the once daily regimen as compared to no adverse effects in the tid regimen. The adverse effect was not consequential to the patient. Statistically, the trough concentrations were not significantly different between the regimens, although the peak concentrations of the once daily regimen were significantly higher.

Conclusions: In conclusion, it can be said that the once daily regimen can be prescribed for Indian patients with epilepsy.

Key Words: Phenytoin, Dosing, Serum, Trough, Peak

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 is being prescribed at various dosages. Many physicians, for fear of the adverse effects and the toxicity of phenytoin, advocate multiple frequency dosing. This fear may be because phenytoin has zero order kinetics.

Initially, phenytoin was administered in 2-4 divided doses throughout the world. Later, pharmacokinetics brought to light the drug half-lives and information on how these could be used to optimize the dosage regimens. Phenytoin has a variable, dose dependent half-life, but the mean is approximately 22 hours [1]. Due to this relatively long half-life, questions were asked. Can phenytoin be given as a once daily dose? What effect will this have on the blood levels and the clinical toxicity profile of the patients? A further point which had to be considered was that a thrice-daily regimen often led to greater non-compliance than a once daily regimen [2].

Various studies which were done abroad [3,4,5] showed that once daily regimens could be given to epileptic patients. This information couldn't be transcribed directly to the Indian patients, since for some compounds, the metabolism differed between the eastern and the Western patients [6].

This paper reports the results of a preliminary study which was done to assess the feasibility of a 300mg once daily dose of phenytoin as compared to a 100mg thrice daily dose in relation to the adverse effects as well as the peak and trough serum levels of Phenytoin.

SUBJECTS AND METHODS:

Study Design

A prospective, randomized, double blinded, crossover study

Sample Size

Based on previous data [7], the mean (±SD) serum level was found to be 10.0 μg/ml (± 5.3). By allowing upto a 3 μg/ml difference as being similar (equal), and by taking the alpha and beta errors at a 5 % and 20% level, the sample size for a crossover study was calculated to be 48 patients in each arm. However, it being a cross over study, 24 patients were needed in total.

Inclusion Criteria

1. Patients between 18 years and 55 years of age.
2. Patients who received a total of 300mg phenytoin as Eptoin daily, for at least one month prior to their entry in the study.

Exclusion Criteria

1. Abnormal liver or kidney functions.
2. Patients who had seizures within one month prior to their entry into the study.
3. Patients having other systemic diseases.
4. Patients who were on any other anticonvulsant drugs concurrently.
5. Patients who were on other drugs which produced an interaction, such as chloramphenicol. disulfiram, isoniazid, dicoumarol and sulfonamides.

Methodology

- The ethical and research committee clearance was sanctioned, following which 24 patients were enrolled into the study, based on the inclusion and exclusion criteria.
- Detailed explanations and implications of the study were given to the subjects and their relatives. Their informed consent was taken. Their liver and renal functions were checked. Their basal phenytoin levels were also estimated. Once these preliminary steps were undertaken and everything was found to be normal, the patients were inducted into either of the 2 treatment arms, based on a random allotment. Each arm was given for a two-week period, after which a crossover format was followed. The treatment arms which were followed were:

  Schedule A: Morning - One dose of 300mg Phenytoin + One 100mg placebo

  Afternoon - One 100mg placebo

  Night - One 100mg placebo

  Schedule B: Morning - One dose of 100mg Phenytoin + One 300mg placebo

  Afternoon - One dose of 100mg Phenytoin

  Night - One dose of 100mg phenytoin
- A double blinded protocol was followed throughout the study. The patients were asked to report to the hospital at the end of the two-week treatment arms. During that time, the compliance cards which were given to them beforehand were checked. Once full compliance of the prescribed regimen was assured, the trough and peak serum concentrations of Phenytoin were measured. During the assumed peak concentration period, a detailed neurological evaluation was conducted to determine the features of the peak level toxicity of Phenytoin. If any patient was found to have such a feature, the patient was withdrawn from the study in accordance with the ethical guidelines.

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

Procedure for Measuring the Drug Levels in Plasma

The concentration of phenytoin was measured by the method of Dill [8]. The serum specimens were collected and kept frozen until they were analyzed . The high and low quality controls were stored alongside the patients' specimens. This ensured that the standards, quality controls and the specimens were kept under the same conditions.

RESULTS

No	Age (yrs)	sex	Height (cm)	Weight (kg)
1	20	M	174	55
2	21	M	170	55
3	25	M	177	55
4	20	M	163	46
5	19	M	163	45
6	35	M	153	55
7	25	M	154	56
8	46	M	157	60
9	34	M	162	58
10	23	M	157	38
11	19	F	160	45
12	32	M	168	51
13	40	F	157	70
14	25	M	167	47
15	21	M	164	44
16	27	M	167	47
17	26	F	157	38
18	46	F	157	55
19	19	M	170	56
20	30	F	158	90
21	30	M	172	60
22	27	M	168	70
23	20	M	154	58
24	21	M	156	58

[Table/Fig-1]: Baseline characteristics of the study participants

Adverse Effects

Regimen A (300mg once daily) – 1/24 - One patient had dizziness and nystagmus

Regimen B (100mg tid) – 0/24

Serum Levels

The mean, SD and the P values were obtained by the Per Protocol and the ITT (Intention to Treat) analysis of the trough and peak serum levels by using Wilcoxon's signed rank test [Table/Fig 2].

Inference

There seemed to be very little difference in terms of the adverse effects between both the regimens. The patient who developed an adverse effect with 300mg once daily had only a mild dizziness and nystagmus, which may not have been a problem if the patients had taken a night dosage.

At 5% level of significance, there was no difference between the trough levels of both the regimens.

At 5% level of significance, there was a difference between the peak levels of both the regimens, with the 300mg once daily regimen having a higher peak level. The clinical relevance of the difference in the peak levels was however diminished, since the adverse effect profile of both the regimens had very little to distinguish between them.

Level (μg/ml)	PER PROTOCOL (n = 22)			ITT (n = 24)		
	A (300mgod)	B (100mgtid)		A (300mgod)	B (100mgtid)	
	Mean (SD)	Mean (SD)	P value	Mean (SD)	Mean (SD)	P value
Trough	16.4 (4.5)	14.9 (3.2)	0.08	16.4 (4.4)	15.1 (3.1)	0.13
Peak	21.4 (5.6)	18.8 (3.9)	0.01	21.4 (5.4)	19.0 (3.8)	0.01

[Table/Fig-2]: Mean trough and peak levels of phenytoin

24 patients were enrolled into the study. One patient was withdrawn from the study due to development of nystagmus. Another patient was lost to follow up.

DISCUSSION

It has been thought that the administration of the daily dose requirement once a day could produce peak serum concentrations which were associated with the toxicity of phenytoin. A peak absorption usually occurs four to 8 hours following phenytoin administration of the drug. Another reason which was given for the reticence in prescribing a once a day dosage was that the serum trough concentrations could become sub-therapeutic. This could lead to breakthrough seizures. The specimen samples for the drug assays were obtained at 4 hours and 24 hours after the drug was administered.

This study showed that there was no significant difference between the trough levels of both the regimens. Therefore, a once daily dose had not led to sub-therapeutic trough concentrations.

There was a significant statistical difference between the peak concentrations of the 2 dosage regimens, with the 300-mg once daily regimen having a higher mean peak value. The clinical significance of this with regards to the toxic effects was however diminished, since the adverse effect profile of both the dosage regimens were similar. Buchanan et al., [9] also supported the finding, that the average level which was obtained 4 hours after the administration of phenytoin (11.95 μg/ml) approximated the average level which was obtained just prior to the dosage (11.49 μg/ml), with 300mg of phenytoin being given as a single dose. In another study, he had indicated that the Css mean was 8.23μg/ml for the single daily dose group and that it was 8.83 μg/ml for the divided dose group. Statistical testing demonstrated no difference between the two levels [3]. In the current study, out of 24 cases, eight subjects had a Cmax above 20 μg/ml in the single dose regimen, as compared to 3 who were on the divided dose regimen. Amongst those patients whose Cmax was above the therapeutic range, only one patient presented with a complaint of mild toxicity from the single dose group.

Buchanan et al., [9] indicated that out of 13 patients, only one had a Cmax within the range of 20-25 μg/ml. On neurological examination, except for significant nystagmus, no other signs of toxicity were found and the patient did not complain of any side effects. It was found that this patient had persistent plasma levels which were in the toxic range, on admission and throughout the study, while 300 mg of phenytoin was given a single dose. In another study [10], he found that more episodes of nystagmus were recorded for the single dose group than for the divided dose group. However, the incidence of nystagmus for both the groups exceeded the levels which were seen in the clinical practice. Nystagmus occurred mostly at or above a serum level of 20 μg/ml. But none of these patients even approached this value. So, a particular correlation between the blood levels and the nystagmus could not be detected there.

The single dose administration of phenytoin has the clinical application of motivating the patients to comply with their dosage schedule as instructed. Motivation and compliance are known to be the problem areas [11]. This may be because active adults and school age children may find it inconvenient to take medications periodically throughout the day. Finally, the single dose administration could decrease the nursing costs for an institution which cared for a large number of epileptic patients.

This study indicated that the two dosage schedules were pharmacologically equivalent. However, the prescribing physician for each individual patient must make the final decision concerning the frequency of the dosage.

LIMITATIONS OF THE STUDY

This study was conducted in an outpatient setting. If this had been conducted in an inpatient department, the time at which the tablet was taken during the entire study period could have been recorded and other issues which were in compliance of the medication could have been brought out.

In this study, the blood samples were taken at only two time points, that is, at the peak and the trough times. These two time points were the basic minimum and they were adequate to achieve the objectives of this study. However, in a kinetic study, it would have been ideal to take repeated samples so that the AUCs could be measured. This would make the study complete and provide comprehensive evidence to support the final inference

In this study, the phenytoin levels were assayed only in the blood. The levels of phenytoin and its metabolite could have been assayed in the urine also. Measuring serum protein would have been helpful in ruling out malnutrition and other co-morbidities which could interfere with the phenytoin levels.

The sample size for this study was small. Having a larger sample size would have provided more support to the inference and it would have possibly uncovered more adverse effects.

CONCLUSION

This study indicated that one could be able to prescribe Tab Phenytoin 300 mg once daily to the Indian patients as an alternative to 100 mg tid, since the adverse effects and the trough level profiles were not significantly different between the two regimens. A once daily regimen could dramatically improve the compliance of the patient. For a chronic disease like epilepsy, patient compliance is important in the overall control of the disease, the quality of life and in the prevention of the complications. It is hoped that the findings of this study will help in the overall management of the epileptic patients in India.

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AUTHOR(S):
1. Dr. S. Bhuvaneshwari
2. Dr. Sujith Chandy
3. Dr. Sudhir Kumar

PARTICULARS OF CONTRIBUTORS:
1. Department of Pharmacology, Christian Medical College, Vellore, India.
2. Department of Neurology, Christian Medical College, Vellore, India.
3. Department of Clinical Pharmacology, Christian Medical College, Vellore, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. S. Bhuvaneshwari
A3, Fourth Floor, Ranga Castle, Kannapiran Mill Road,
Sowripalayam, Coimbatore, India - 641028.
Phone numbers: 98655 61463
E-mail: su_bhuvans@yahoo.co.in

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