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Research Article

EFFECT OF MENSTRUAL CYCLE PHASES ON PHARMACOKINETICS OF PHENYTOIN IN EPILEPTIC PATIENTS

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Abstract

Epilepsy is a characteristic neurological disorder of recurrent seizures of cerebral origin. In female epileptic patients, seizure frequency doubles at the time of menstruation which is often called as Catamenial Epilepsy. The cyclic changes of menstrual cycle alter the pharmacokinetics of the anti-epileptic drugs. In the present study, the Phenytoin levels in the salivary samples of female epileptic patients are estimated by HPLC method. In order to study the alterations in the pharmacokinetics of phenytoin, various pharmacokinetic parameters like AUC, C_{max}, Elimination Half life, volume of distribution, mean clearance can be determined. The results of the study shows mean salivary levels of phenytoin were lower in follicular phase compared to ovulatory phase could be the reason for precipitating seizures during menses in catamenial epileptic patients. Hence dosage adjustments may be made for better management of disease. At the same time, the levels being monitored cautiously because of its narrow therapeutic index and enzyme saturation kinetics.

Key words: Epileptic patients – HPLC – Menstrual cycle – Pharmacokinetics – Phenytoin – Salivary samples.

Introduction

Epilepsy is a chronic neurological disorder characterized by recurrent seizures of cerebral origin, presenting with episodes of sensory, motor or autonomic phenomenon with or without loss of consciousness. An increase in seizure frequency around the time of menstruation was first documented more than 100 years ago and in 1/3 of

women, seizure frequency more than doubles at certain times of the cycle. This is often called catamenial seizure exacerbation or catamenial epilepsy. Three distinct patterns of catamenial epilepsy described are perimenstrual, periovulatory and inadequate luteal phase catamenial seizures [1]. It affects up to 70% of women with epilepsy and catamenial seizures are common among women with focal or generalized epilepsy [2]. Estrogen and progesterone are two hormones that affect the excitability of brain cells, estrogen tends to excite them, whereas progesterone calms them. During the course of a menstrual cycle, the levels of these hormones change in the blood. The progesterone metabolite, allopregnanolone is identified as endogenous neurosteroid with powerful antiseizure activity which is a potent, positive allosteric modulator of GABA-A receptors [2].

Ovarian hormones alter physiological functions and thereby modifies the pharmacokinetics of drugs which inturn modulate pharmacodynamics. The level of female hormones is phase specific and the pharmacokinetic parameters of drugs are altered by the cyclic changes in menstrual cycle i.e., luteal phase has high levels of progesterone which relaxes gastrointestinal smooth muscle, alters gastrointestinal transit time and drug absorption [3]. Follicular phase has higher circulating levels of α-1 acid glycoprotein [4] increases protein binding and decreases free drug concentration. Gender exerts influence on the clearance of some drugs by regulating cytochrome P450 isoenzymes [5, 6]. Estrogens inhibit the metabolism of many drugs by inhibiting liver microsomal enzymes [7], whereas progesterone has both inhibitory and inductive effect [8, 9].

Variability in pharmacokinetics during different phases of menstrual cycle is demonstrated with various drugs such as Propronolol [10], Triazolam [11], Theophylline and Amikacin [12], Paracetamol [13], Indocyanine green [14], Nitrazepam [15], Alprazolam [16] and Ranitidine [17].

The objective of this study was to examine the pharmacokinetic profile of antiepileptic drug, Phenytoin as a function of different phases (i.e., follicular phase, ovulatory phase and luteal phase) of the menstrual cycle which is inturn linked with seizures. Phenytoin was selected for the study as it has narrow therapeutic index and complex pharmacokinetic properties. Drug concentration maintenance plays a vital role in drugs with narrow margin of safety to overcome the therapeutic failure on one hand and to decrease the adverse effects on the other hand.

Further, large inter-individual variation, concentration dependent pharmacokinetics, high protein binding and delayed detection of toxicities are prerequisites for therapeutic drug monitoring.

Saliva is used for the monitoring of systemic levels of drugs, as it offers distinctive advantages over serum [18, 19]. The concentration of most drugs in saliva corresponds to the free or unbound plasma drug concentrations [20-23] and the concentration of drugs in saliva is proportional to the concentration in plasma [24-26]. A good correlation is observed between serum and salivary levels of Phenytoin, Phenobarbital and Carbamazepine [27]. In our study, salivary levels of phenytoin in catamenial epileptic patients were estimated during three phases of menstrual cycle for the evaluation of pharmacokinetic parameters.

Patients and Methods

20 female epileptic patients with their body weights ranging from 40 to 60 kgs, height 140 to 160 cms and age 21 to 45 years were included in the study. The study protocol was approved by Institutional Ethical Committee. Patients with regular menstrual cycle, not suffering from any other chronic disease except epilepsy (Catamenial) and not using any other drug except Phenytoin were included in the study after obtaining written informed consent. Patients with a history of cardiac, pulmonary, hepatic, renal, haematologic or endocrinologic disorders or having irregular menstrual cycles, suffering from amenorrhea or women using oral contraceptive pills were excluded from the study.

Patient selection:

The female epileptic patients were selected from the patients who visited Neurology department as out patients in the Guntur General Hospital, Guntur, after taking due permission from that department and written informed consent was obtained from all the patients who were willing to participate in the study. 20 female epileptic patients who complied inclusion criteria and on long term oral Phenytoin monotherapy (not less than 2 years) with prescribed dosage regimen as per physician's prescription (100 mg morning and 200 mg in the night) were selected for the study. Salivary samples were collected from each patient prior to the morning dose (0 h) and at the time points of 1, 2, 3, 4, 6, 8 & 12 hours after dosing. Salivary samples were collected after cleaning the

tongue debris and mouth every time before sampling, which were stored at -80°C until further analysis. Salivary samples containing Phenytoin were measured by HPLC method, on reverse phase C -18 column with a total analytical time less than 6.5 minutes [28].

Chromatographic conditions:

Mobile phase consisting of methanol: water: glacial acetic acid (67: 33: 1 v/v/v) was prepared and mixed thoroughly, degassed and used for the HPLC analysis. 1.0 ml per minute flow rate was maintained throughout the analysis. The eluent was monitored using a UV-VIS detector set at 230 nm and sensitivity was set at 0.001 a.u.f.s.

Preparation of standard graph:

Standard solutions:

Stock solutions of 100 µg/ml each of Phenytoin and Carbamazepine were prepared in methanol. These solutions were further diluted with methanol to the required concentrations of each drug. All solutions were stored at – 4ºC. For the preparation of standard graph 0.1, 0.5, 1, 5, 10, 50 and 100 µg/ml of Phenytoin in saliva was used.

Patient saliva extraction procedure:

To each 100 µl of saliva sample, 20 µl of internal standard (500ug/ml Carbamazepine solution) was added and extracted with 1.7 ml of ethyl acetate, vortexed for 1 min and centrifuged at 13,000 rpm for 8 min. The supernatant was evaporated to dryness and the residue was reconstituted with 100 µl of mobile phase, vortexed for 1 min. and 20ul was injected onto HPLC. The standard solutions were also processed by similar extraction procedure. The retention times were 5.1 min. and 6.0 min. for Phenytoin and Carbamazepine respectively. The peak area ratios obtained at different concentrations of the drug were plotted against the concentrations of the drug. The slope of this plot was calculated by least squares regression analysis and was used to calculate Phenytoin concentration in unknown salivary samples. Data was analyzed for pharmacokinetic parameters by using RAMKIN software.

Mean Cmax and T_{max} values were obtained directly from concentrations and time data and various pharmacokinetic parameters for Phenytoin were obtained in each patient from saliva concentration versus time data.

Statistical analysis:

All the results were expressed as mean ± S.D and data was analyzed using one way ANOVA followed by Newman-Keuls multiple comparison test. A value of $P < 0.05$ was considered to be statistically significant.

Analysis of blank blood samples for hormones:

The blank blood samples were collected from the patients before administration of the drug (0h) and analyzed for concentrations of estrogen and progesterone hormones by the Chemiluminisence method.

Results:

The mean salivary Phenytoin levels versus time following the three phases of menstrual cycle were shown in Fig.1, salivary Phenytoin levels were higher in the ovulatory phase than in follicular phase and its levels in the follicular phase were between those for ovulatory and luteal phase. Mean concentrations of estrogen and progesterone in three phases of menstrual cycle were summarized in table 1. Mean values of various pharmacokinetic parameters of Phenytoin obtained in three phases (Table 2) were compared with the values obtained in other two phases and for the calculation of percentage increase or decrease, follicular phase was treated as reference (Table 3).

Fig.1. Mean salivary concentration versus time profile of Phenytoin during three phases of menstrual cycle in epileptic patients

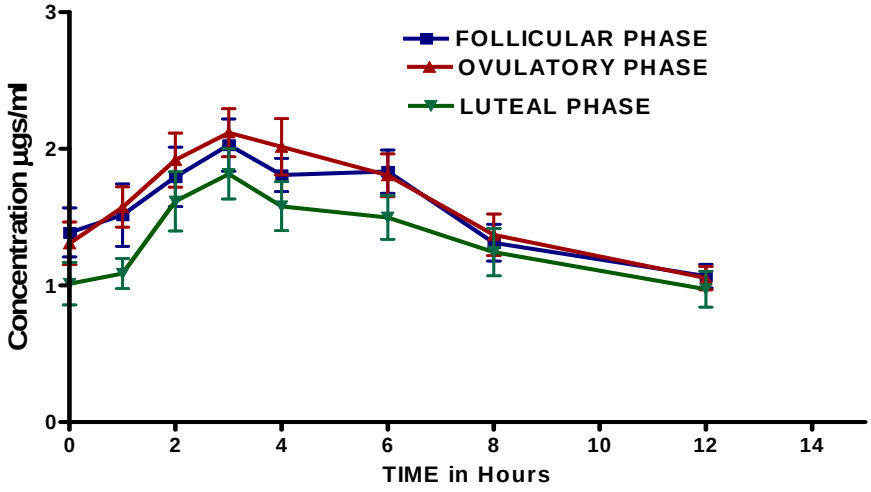

Table 1: Mean levels of hormones in epileptic patients using Phenytoin in three phases of menstrual cycle (n=20)

Hormone	Follicular phase	Ovulatory phase	Luteal phase
Estrogen (pg/ml)	34.54 ± 21.26	105.3 ± 120.2	108.5 ± 90.8
Progesterone(ng/ml)	0.9 ± 0.5	5.8 ± 3.9	10.9 ± 8.9

Table 2: Pharmacokinetic parameters of Phenytoin during three phases (n=20)

Pharmacokinetic parameter	**Follicular phase Mean ± SD**	**Ovulatory phase Mean ±SD**	**Luteal phase Mean ±SD**	**Statistical significance**	**p-value**
Cmax (ug/ml)	2.32 ± 0.87	2.42 ± 0.93	2.08 ± 0.91	NS	0.4934
Tmax (hrs)	3.65 ± 1.42	3.85 ±1.46	3.75 ± 1.29	NS	0.9024
AUC_{0-t} (ug/ml/hr)	18.77 ± 6.49	19.12 ± 6.64	16.39 ± 7.48	NS	0.3311
$AUC_{0-\infty}$ (ug/ml/hr)	50.80 ± 34.20	40.46 ± 27.60	42.80 ± 43.82	NS	0.6348
$AUMC_{0-\infty}$ (ug/ml/hxh)	2554.31 ± 3767.12	1219.66 ± 2659.34	1844.90 ± 3488.20	NS	0.4542
$t_{1/2}$(hrs)	22.47 ± 22.44	12.78 ± 11.90	15.92 ± 15.77	NS	0.2029
Vd/f (ml/kg)	3749.37 ± 3805.61	2656.89 ± 1095.45	3488.15 ± 1559.18	NS	0.3471
Vss/f (ml/kg)	4245.40 ± 4603.61	3006.59 ± 1066.66	3950.52 ± 1504.55	NS	0.3665
CLs/f(ml/hr/kg)	171.85 ± 100.17	188.51 ± 91.49	239.59 ± 138.77	NS	0.1467
MRT(hr)	34.90 ± 33.75	20.27 ± 16.82	24.95 ±22.49	NS	0.1851
Ka (h^{-1})	0.166 ± 0.133	0.191 ± 0.116	0.189 ± 0.110	NS	0.7995

Table 3: Percentage changes in pharmacokinetic parameters of Phenytoin in different phases of menstrual cycle

Pharmacokinetic parameter	Follicular phase	Ovulatory phase	Luteal phase	Statistical significance	p-value
Cmax (ug/ml)	2.32 Reference	2.42 4.31 % ↑	2.08 10.34 % ↓	NS	0.4934
Tmax (hrs)	3.65 Reference	3.85 5.47 % ↑	3.75 2.73% ↑	NS	0.9024
AUC_{0-t} (ug/ml/hr)	18.77 Reference	19.12 1.91 % ↑	16.39 12.68 % ↓	NS	0.3311
$AUC_{0-\infty}$ (ug/ml/hr)	50.80 Reference	40.60 20.35 % ↓	42.80 15.73 % ↓	NS	0.6348
$AUMC_{0-\infty}$ (ug/ml/hxh)	2554.31 Reference	1219.66 52.25 % ↓	1844.90 27.77 % ↓	NS	0.4542
$t_{1/2}$ (hrs)	22.47 Reference	12.78 43.1 % ↓	15.92 29.14 % ↓	NS	0.2029
Vd/f (ml/kg)	3749.37 Reference	2656.89 29.13 % ↓	3488.15 6.96 % ↓	NS	0.3471
Vss/f (ml/kg)	4245.40 Reference	3006.59 29.17 % ↓	3950.52 6.94 % ↓	NS	0.3665
CLs/f(ml/hr/kg)	171.85 Reference	188.51 9.68 % ↑	239.59 39.4 % ↑	NS	0.1467
MRT(hr)	34.90 Reference	20.27 41.93% ↓	24.95 28.51% ↓	NS	0.1851
Ka (h^{-1})	0.166 Reference	0.191 15.06 % ↑	0.189 13.85 % ↑	NS	0.7995

None of the above changes pertaining to the pharmacokinetic parameters attained statistical significance ($P > 0.05$) because of larger inter-individual variation.

Discussion:

Mean serum Phenytoin levels were lower during menses (early follicular phase) in women with catemenial epilepsy compared to women with noncatemenial epilepsy due to increased clearance of Phenytoin. However, the ovulatory phase Phenytoin levels were increased as hepatic metabolism was slowed due to competition with steroid

hormones [29]. In the present study, though non-significant, mean salivary levels of Phenytoin in follicular phase were lower compared to ovulatory phase.

The mean AUC and elimination half life of Antipyrine was significantly smaller and mean clearance was significantly greater on 15^{th} and 21^{st} day when compared to 5^{th} day of menstrual cycle [30]. In our study, though not significant, similar results were found with Phenytoin i.e., mean $AUC_{0-\infty}$ and half-life were smaller, mean clearance was greater in ovulatory and luteal phases when compared to follicular phase. In females with normal regular menstrual cycle of 28 days, estrogens and progesterones are lower at the beginning of the cycle, the estrogens reach a peak just before ovulation and once again in the mid luteal phase [31]. Similarly, mean concentrations of estrogen were increased in ovulatory and luteal phases compared to follicular phase in epileptic patients using phenytoin in our study. The shortening of half-life and increase in clearance could be due to estrogen-progesterone surges in mid-cycle.

Blackham and Spencer [9] reported that estrogens prolonged while progestogens reduced drug metabolism. The circulating levels of a number of hormones including estradiol, luteinizing hormone, follicle stimulating hormone and prolactin, change dramatically around the time of ovulation and this could affect the hepatic metabolism of drugs in women [32].

Backstrom and Jorpes [33] reported that there was no variation in either serum albumin concentration or in the extent of protein binding of Phenytoin, Phenobarbital and Carbamazepine during the menstrual cycle. In contrast, though not significant, volume of distribution of Phenytoin was decreased in ovulatory and luteal phases when compared to follicular phase in the present work.

The bioequivalence studies of Williams et al., [34] indicate, an increased bioavailability reflecting an increased $AUC_{0-\infty}$ value. In fact the mid-cycle $AUC_{0-\infty}$ value of Methaqualone was smaller than that obtained at the beginning of the cycle indicated the predominant pharmacokinetic change at this stage of the menstrual cycle, increased rate of metabolite formation and hence clearance [32]. Similar $AUC_{0-\infty}$ value was obtained with Phenytoin.

Bruguerolle and coworkers examined the pharmacokinetics of Theophylline in asthmatics on 0^{th}, 10^{th} and 20^{th} days of the menstrual cycle and found that the maximum plasma drug concentration, minimum mean resident time and elimination half life occurred at mid-cycle [35]. Similar results were found with Phenytoin in our study.

The elimination half-life of Acetaminophen reported to be shorter in the mid-phase of the menstrual cycle [36]. Absorption of drugs from the small intestine increased during the luteal phase because of the prolonged gastrointestinal transit time [37]. Relatively high levels of progesterone promote smooth muscle relaxation and prolong gastrointestinal transit time [38]. In the present study Phenytoin's $AUC_{0-\infty}$ i.e., the rate and extent of absorption was increased during the luteal phase than the ovulatory phase.

Significant changes in endogenous sex hormone concentrations occur during the menstrual cycle and pregnancy, leading to alterations in protein binding, distribution and clearance [39]. The volume of distribution of Phenytoin was decreased in ovulatory and luteal phases compared to follicular phase.

Comparison of data obtained in follicular phase and luteal phase revealed difference in most pharmacokinetic parameters, indicative of the characteristic physiological changes associated with the luteal phase that largely affect the kinetics and availability of Ranitidine [17]. AUC and C_{max} of Ranitidine was decreased, clearance was increased in luteal phase compared to follicular phase. Similar changes were observed with Phenytoin in our study.

Large fluctuations in hormone concentrations throughout the menstrual cycle potentially impact hepatic enzyme activity and affect the metabolism of drugs. Progesterone has been shown to both inhibit and induce hepatic enzyme activity [37]. In our study, the increased clearance of Phenytoin in the luteal phase is probably due to progesterone's induced hepatic enzyme activity. This value did not attain significance due to large inter individual variability. Estrogen decreases oxidative drug metabolism through inhibition of certain cytochrome P450 enzymes and inhibits the hepatic clearance of Imipramine [40]. In our study, the decreased clearance of Phenytoin though non-significant in the ovulatory phase than luteal phase may be due to peak estrogen levels in ovulatory phase.

Inter and intra-patient variation in the AUC (extent of absorption) is possibly due to variation in estrogen levels. However, a significant negative relationship was found between AUC and estradiol levels, suggesting that Zidovudine glucuronidation change in relation to the menstrual cycle phase [41]. Similar results i.e. negative relationship between $AUC_{0-\infty}$ of phenytoin and estradiol levels was observed in this study.

In the Amikacin study, clearance and volume of distribution were highest in the mid-luteal phase, while elimination half life was not altered, due to phase related changes in estrogen and FSH levels were correlated with its pharmacokinetic parameters. In the follicular phase, the FSH levels correlated with the CL_{total} of the drug and in luteal phase, progesterone levels were highly correlated with CL_{total}. In our study Phenytoin clearance increased and was highest in luteal phase due to high concentrations of progesterone in our epileptic patients similar to Amikacin.

Conclusion

Though Non-significant, mean salivary levels of Phenytoin were lower in follicular phase compared to ovulatory phase could be the reason for precipitating seizures during menses in catamenial epileptic patients. Hence dosage adjustments may be made for better management of the disease. At the same time, the levels being monitored cautiously because of its narrow therapeutic index and enzyme saturation kinetics.

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