

Effect of age and sex on serum phenytoin concentration in epileptic patients: experience from therapeutic drug monitoring

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Received: 18 May 2019

Accepted: 02 July 2019

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ABSTRACT

Background: Phenytoin is a widely prescribed anticonvulsant drug. There is a wide interpatient as well as inpatient variability in serum phenytoin levels despite standard doses. Phenytoin dosing is challenging because the drug exhibits nonlinear kinetics and interacts with a number of drugs. Children metabolize the drug faster as compared to adults. Ageing is also associated with progressive decline in phenytoin clearance. Many CYP450 enzymes show a sex-dependent difference in activity. The objective for this study was to find the effects of sex and ageing on serum phenytoin levels.

Methods: The influence of sex and ageing on the serum phenytoin levels was evaluated retrospectively in 96 anonymized epileptic patients who had received phenytoin alone for more than four weeks. These patients were divided into three age groups, up to 18 years (children), 19-60 years (adults) and more than 60 years (elderly).

Results: There were 6.25% children, 84.37% adults and 9.37% elderly. The majority (71.87%) of patients were males. Children achieved a mean phenytoin level of 15.71 ± 4.85 µg/ml after a daily dose of 225.00 ± 75.82 mg. Adults attained a mean serum phenytoin level of 16.12 ± 3.90 µg/ml with a mean daily dose of 282.72 ± 69.44 mg. The elderly achieved a mean serum phenytoin level of 15.85 ± 2.19 µg/ml after a mean daily dose of 266.67 ± 70.71 mg. As compared to 77.77% females, 84.05% males had phenytoin levels in therapeutic range. 50.00% children, 82.71% adults, and 100.00% elderly had phenytoin levels in therapeutic range. There was a correlation between sex, age and serum phenytoin levels ($r = 0.003$ to 0.762).

Conclusions: There was a correlation between sex, age and serum phenytoin levels in this study. A better understanding of the effects of sex and age on the clinical pharmacology of phenytoin would enhance the quality of prescribing.

Keywords: Age, Epilepsy, Phenytoin, Serum level, Sex, Therapeutic drug monitoring

INTRODUCTION

Therapeutic drug monitoring (TDM) is based on the principle that for some drugs there is a close relationship between the plasma level of the drug and its clinical effect. Standard or empirical methods of dosing are appropriate for most of the drugs.¹ TDM is used mainly for monitoring drugs with narrow therapeutic ranges and marked pharmacokinetic variability.²

Phenytoin is one of the commonly used drugs for the management of epilepsy in all age groups.³ It has certain physicochemical characteristics which make it liable to bioavailability problems.⁴ Phenytoin dosing is challenging because the drug exhibits non-linear pharmacokinetics, zero-order elimination, and a multitude of drug-drug interactions. For this reason, drug levels are measured to optimize dosing.⁵ Males and females differ in drug disposition and response.⁶ The ageing process is

characterized by structural and functional changes affecting all organ systems. Changes in body composition, hepatic and renal function are responsible for prolongation of plasma half-life. Significant pharmacodynamic changes also occur which; in general, tend to increase sensitivity to drugs.⁷

The aim of this study was to study the relationship between sex, age and serum phenytoin levels in epileptic patients and also the relationship between dose and serum phenytoin levels. This knowledge of the behavior of serum phenytoin concentration in individual patients in relation to sex, age and dose would enhance the quality of prescribing.

METHODS

We retrospectively evaluated 300 anonymized TDM analyses of patients who had received phenytoin alone for more than 4 weeks. All data were derived from the database of the therapeutic drug monitoring service of a tertiary care hospital. 96 patients fulfilling the inclusion criteria were divided into three groups: children (1-18 years), adults (19-60 years) and elderly (>60 years).³ Most studies and reviews on the subject have considered the elderly to be 65 years or older, but some have included persons over the age of 60.⁸ The exclusion criteria included samples drawn for evaluating the peak levels; samples from suspected cases of non-compliance or overdose; and, samples from patients with severe renal and/or hepatic disorders.³

The total serum phenytoin concentration was measured by a calibrated and validated semi auto analyser (EMIT) made by Transasia India and reagent used was made by Siemens Healthcare USA. Drug levels were categorized into sub-therapeutic (<10 µg/ml), therapeutic (10-20 µg/ml), supra-therapeutic (20-40 µg/ml).³ Age and sex, recorded at the time of blood sampling were used to assess the influence of these physiological factors on serum phenytoin concentration.⁹

Statistical analysis

After the completion of data collection, it was analysed to check identifiable errors and incompleteness. The data was analysed by Statistical Package for the Social Sciences (SPSS) version 20.

RESULTS

Males

Constituted 71.87% of study population (n=69) and the mean age was 37.77±16.32 years (Table 1). Mean dose was 268.52±66.72 mg/day and mean phenytoin level was 16.08±3.53 µg/ml (Table 2). 5.79% patients (n=4) had sub therapeutic serum phenytoin levels, 84.05% (n=58) therapeutic and 10.14% (n=7) supra-therapeutic levels (Table 3). Pearson correlation between dose and level was weak (r=0.195) and the correlation between age and level was also weak(r=0.043) (Table 4).

Table 1: Characteristics of study population(n=96).

Group	Male	Female	Total	Min. age	Max. age	Mean age±SD
Total	69 (71.87%)	27 (28.12%)	96 (100.00)	3	80	38.60±16.41
Up to 18 years	4	2	6 (6.25%)	3	18	13.17±5.70
19-60 years	59	22	81 (84.37%)	19	60	37.00±12.39
>60 years	6	3	9 (9.37%)	65	80	70.00±4.84

Table 2: Daily dose and serum phenytoin concentration in different groups.

Group	Daily dose (mg/Day)			Measured serum level (µg/ml)		
	Min	Max	Mean±SD	Min	Max	Mean±SD
Males Total	100	400	268.52±66.72	7.00	25.00	16.08±3.53
Females Total	100	400	282.60±71.65	8.00	26.00	16.06±4.51
Up to 18 years	100	300	225.00±75.82	9.00	21.50	15.71±4.85
Males	100	300	212.50±85.39	9.00	20.20	15.30±2.35
Females	200	300	250.00±70.71	11.60	21.50	16.55±4.95
19 to 60 years	100	400	282.72±69.44	7.00	26.00	16.12±3.90
Males	100	400	288.98±68.27	7.00	25.00	16.23±3.58
females	100	400	265.91±71.35	8.00	26.00	15.82±4.73
>60 years	100	300	266.67±70.71	11.00	18.00	15.85±2.19
Males	100	300	250.00±34.15	11.00	17.00	15.03±2.23
Females	300	300	300.00	16.50	18.00	15.85±2.19

Table 3: Serum Phenytoin levels in different groups.

Group	Sub-therapeutic level	Therapeutic Level	Supra-therapeutic
Males (n=69)	4 (5.79%)	58 (84.05%)	7 (10.14%)
Females (n=27)	3 (11.11%)	21 (77.77%)	3 (11.11%)
Total (n=96)	7 (7.29%)	79 (82.29%)	10 (10.41%)
Children (n=6)	1 (16.66%)	3 (50.00%)	2 (33.33%)
Adults (n=81)	6(7.40%)	67 (82.71%)	8 (9.87%)
Elderly (n=9)	-	9 (100.00%)	-

Table 4: Pearson correlations (r) of different variable pairs.

Group	Pair	r
Males	Age and level	0.043
	Dose and Level	0.195
Females	Age and level	0.120
	Dose and Level	0.443
Children	Age and Level	0.737
	Gender and level	0.133
	Dose and Level	0.762
Adults	Age and level	0.084
	Gender and Level	0.046
	Dose and level	0.231
Elderly	Age and Level	0.110
	Gender and Level	0.562
	Dose and Level	0.118
Overall	Age and Level	0.068
	Gender and Level	0.003
	Dose and Level	0.269

Females

Constituted 28.12% of study population (n=27) and the mean age was 40.74±16.76 years. (Table 1). Mean dose was 282.60±71.65 mg/day and mean drug level was 16.06±4.51 µg/ml (Table 2). 11.11% patients (n=3) had sub therapeutic serum phenytoin levels, 77.77% (n=21) therapeutic and 11.11 % (n=3) supra-therapeutic levels (Table 3). Pearson correlation between dose and level was moderate (r=0.443) and the correlation between age and level was weak(r=0.120) (Table 4).

Children

Constituted 6.25% of study population (n=6) and the mean age was 13.17±5.70 years (Table 1). Mean dose was 225.00±75.82 mg/day and mean drug level was 15.71±4.85 µg/ml. The mean dose in male children was 212.50±85.39 mg/day and produced a mean level of 15.30±2.35µg/ml. The mean dose in female children was 250.00±70.71mg/day and produced a mean level of 16.55±4.95 µg/ml (Table 2). 16.66% children (n=1) had sub therapeutic serum phenytoin levels, 50.00% (n=3) therapeutic and 33.33% n=2) supra-therapeutic levels (Table 3). Pearson correlation between dose and level

(r=0.762) and age and level (r=0.737) was strong. But the correlation between gender and level was weak(r=0.133) (Table 4).

Adults

Constituted 84.37% of study population (n=81) and the mean age was 37.00±12.39 years (Table 1). Mean dose was 282.72±69.44 mg/day and mean drug level was 16.12±3.90 µg/ml. The mean dose in male adults was 288.98±68.27 mg/day and produced a mean level of 16.23±3.58 µg/ml. The mean dose in female adults was 265.91±71.35 mg/day and produced a mean level of 15.82±4.73 µg/ml (Table 2). 7.40% adults (n=6) had sub therapeutic serum phenytoin levels, 82.71% therapeutic (n=67) and 9.87% (n=8) supra-therapeutic levels (Table 3). Pearson correlation between dose and level was weak (r=0.231) and the correlation between gender and level was also weak(r=0.046) (Table 4).

Elderly

Constituted 9.37% of study population (n=9) and the mean age was 70.00±4.84 years (Table 1). Mean dose was 266.67±70.71mg/day and mean drug level was 15.85±2.19 µg/ml. The mean dose in male adults was 250.00±34.15 mg/day and produced a mean level of 15.03±2.23 µg/ml. The mean dose in female adults was 300.00 mg/day and produced a mean level of 15.85±2.19 µg/ml (Table 2) All the elderly patients had phenytoin levels in therapeutic range (Table 3). Pearson correlation between dose and level was weak (r=0.118) and the correlation between gender and level was strong (r=0.562) (Table 4).

DISCUSSION

Phenytoin dosing is challenging because of capacity-limited metabolism, interindividual variability, ethnic differences and drug interaction with concomitantly-administered medications.⁵ There is not only a wide variation in the serum levels of phenytoin between individual patients, but perhaps even within the same patient at differing times.¹⁰ Differences in metabolism are believed to be the major cause of differential pharmacokinetics between men and women.¹¹ Many CYP450 enzymes show a sex-dependent difference in activity. Activities of these enzymes can also change

during pregnancy and with the use of oral contraceptives. Significant hormonal changes in menopausal and postmenopausal women can also lead to altered drug disposition in women. It is now generally accepted that extremes of age, also have an effect on drug metabolism and clearance. Age-associated reductions in function of some but not all cytochrome P450 enzymes (CYPs) have been described.¹² In elderly pharmacokinetic changes occur in absorption, distribution, metabolism, and

elimination. Gastric secretion, blood flow, and gastrointestinal motility are lower, and these may affect absorption. Reduction in serum albumin levels leads to reduction in protein binding and increase in free fraction of the drug. This is particularly significant for highly protein bound drugs such as phenytoin, carbamazepine, and valproic acid.⁸ Therefore, dosage optimization may be needed to maintain drug efficacy and safety in these subgroups.¹³

Table 5: Significance level of gender differences in different age groups in relation to mean phenytoin dose and mean serum levels.

variable	Children		Adults		Elderly	
	t	p	t	p	t	p
Male vs female (Mean daily dose)	-12.589	0.050	-22.929	0.028	-11.163	0.057
Male vs Female (Mean serum level)	-115.400	0.006	-20.603	0.031	-154.88	0.004

Table 6: Significance level of dose and serum level in different age groups.

Variable	Children vs adults		Children vs elderly		Adults vs elderly	
	t	p	t	p	t	p
Mean dose	-8.898	0.071	-12.015	0.053	-31.545	0.020
Mean level	-48.864	0.031	-33.209	0.019	-22.811	0.028

The present study was conducted to find the effects of age, and gender on serum phenytoin concentration and to find a relationship between phenytoin dose and serum levels achieved. Majority of the patients (82.29%) had phenytoin serum concentration within therapeutic range despite receiving lesser than recommended dose. This could be due to genetically slow metabolism in north Indian population.³ In this study female patients achieved lower serum phenytoin concentration as compared with men despite of higher mean daily dose. Similar findings were seen by Houghton et al.⁹ In one more study it has been reported that women have a lower mean serum phenytoin concentration than men treated with an identical dose/kg of body weight although the difference was not statistically significant.⁹ The correlation between various variables studied and serum concentration was weak to strong.(Table 3) We found a weak positive correlation between serum phenytoin concentration and age. Houghton et al, also found a similar correlation.⁹ authors found most of the patients (82.29%) in therapeutic range. Sangeeta et al. also found maximum number of patients in therapeutic range.³ Author compared mean phenytoin dose and achieved serum levels between males and females in all age groups and found significant differences. (Table 5) authors also compared mean dose and serum levels of different age groups and found significant differences in mean serum levels as shown in (Table 6) As compared to young adults, in elderly the differences were highly significant. Malley et al. also observed that as compared to young adults the elderly have decreased ability to

metabolize drugs and this may contribute to the known high incidence of adverse drug reactions in the elderly.¹⁴

CONCLUSION

Characterizing the pharmacokinetics and pharmacodynamics of a drug in diverse populations is essential in improving therapeutic effectiveness while minimizing adverse events. A better understanding of the effects of sex and ageing on the clinical pharmacology of therapeutic agents would enhance the quality of prescribing. It is concluded that besides various other factors, sex, and age should also be considered for optimal dosing of patients with Phenytoin.

This is a single institution study on a small number of patients and adds to our understanding of effects of sex and age on serum phenytoin levels. But it is difficult to draw a definite conclusion from observations on a small number of patients. The results may not be applicable to the general population. For better understanding of the effects of sex and age on serum phenytoin levels, further multicentre studies involving large number of patients are required.

ACKNOWLEDGEMENTS

The author wishes to thank Danish Shakeel, CSE-IBM student of Chandigarh University, Mohali, Punjab, India for helping in tabulation and statistical analysis of data.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Mir SA. Effect of age and sex on serum phenytoin concentration in epileptic patients: experience from therapeutic drug monitoring. *Int J Basic Clin Pharmacol* 2019;8:1717-21.