RELATIONSHIP BETWEEN BIOCHEMICAL PARAMETERS - LIVER ENZYMES (AST, ALT AND ALP) AND BLOOD PHENYTOIN LEVELS IN PATIENTS OF EPILEPSY

Ashok Binjawadgi[1], Patil B V[2], Shrinivas Raikar[3], Manu Bhardwaj[4], Basavambika Anandi[5], Shivaraj[6]

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ABSTRACT: CONTEXT: Mankind exhibits epilepsy as one of the common neurologic disorders. Standard drug therapy of this disease provides control of seizures in more than 80% of patients. Effective, specific treatment by Anti-Epileptic Drugs becomes absolutely essential for successful treatment in human subjects. Epilepsy especially Grand-Mal variant is typically treated with Phenytoin. Unique point about our study is focused on the estimation of serum phenytoin sodium concentration and to correlate it with some of the important biochemical markers that assess the hepatic function. **AIMS:** 1. It may help to assess whether the epileptic patient receiving phenytoin on an out-patient basis requires an additional dose when monitoring shows suboptimal levels. 2. Should the maintenance dose be reduced, stopped or adjusted to minimize the dose related adverse effects without sacrifice of seizure control. 3. Study also provides an estimation of out-patient compliance. 4. Rational designing of dosing regimen, prediction of future drug concentration and assessment of functional impairment due to disease may be possible. 5. Failure to provide adequate control in maximal tolerated dose by phenytoin after confirming compliance may give a clue to substitute another drug. **METHODS AND MATERIALS:** Thirty seven patients suffering from grand mal epilepsy who attended the neurology OPD of Basaveshwar Teaching and General Hospital were selected for the study. Two patients received 100mg, 25 patients 200mg and 10 patients received 300mg of Dilantin Sodium (Parke Davis) capsule daily at night between 9-10pm. The period of the exposure to the drug varied from 1-5 years. Ten healthy volunteers of same age group who were not receiving any drugs were the control for the study. 10ml of blood was collected from each patient between 9-10am. 2ml of serum was extracted from each sample; serum phenytoin level was measured using UV Spectrophotometer, Bausch and Lomb 21 by the method of Dill. 5ml of blood was collected to measure the following biochemical parameters: Serum AST, Serum ALT, Serum ALP, Instrument – Ciba Corning Blood gas 288 system and other biochemical parameters are measured by Technicon-RA-XT Auto Analyser. **CONCLUSION:** The present study summarizes its findings in patients of grand-mal epilepsy receiving phenytoin therapy. Elevation of serum alkaline phosphatase levels in comparison to the control group. Other parameters such as serum aspartate transaminase and alanine transaminase were within normal limits and there was no significant correlation.

KEY WORDS: Phenytoin, AST, ALT, ALP, Grand-Mal Epilepsy

INTRODUCTION: Mankind exhibits epilepsy as one of the common neurologic disorders. Standard drug therapy of this disease provides control of seizures in more than 80% of patients.[1] Effective, specific treatment by Anti-Epileptic Drugs becomes absolutely essential for successful treatment in human subjects.[2]

Epilepsy especially Grand-Mal variant is typically treated with Phenytoin. Full recovery is rare from the disease process, and patient non-compliance is usually the cause of treatment failure.[3]

Unique point about our study is focused on the estimation of serum phenytoin sodium concentration and to correlate it with some of the important biochemical markers. The kinetics of the drug necessitates this estimation. The aim of our study is therefore the evaluation and validation of various facts from the data and perhaps certain relevant recommendations.

In this study total serum phenytoin level was measured. We have neither measured the levels of free phenytoin in the serum nor have we predicted the value of phenytoin from a ratio of the total phenytoin in the serum and the serum albumin levels.

In this study an attempt is made to correlate serum phenytoin levels with biochemical parameters that assess the hepatic function.

OBJECTIVES:

1. It may help to assess whether the epileptic patient receiving phenytoin on an out-patient basis requires an additional dose when monitoring shows suboptimal levels.
2. Should the maintenance dose be reduced, stopped or adjusted to minimize the dose related adverse effects without sacrifice of seizure control.
3. Study also provides an estimation of out-patient compliance.
4. Rational designing of dosing regimen, prediction of future drug concentration and assessment of functional impairment due to disease may be possible.
5. Failure to provide adequate control in maximal tolerated dose by phenytoin after confirming compliance may give a clue to substitute another drug.

MATERIALS AND METHODS: Thirty seven patients suffering from grand mal epilepsy who attended the neurology OPD of Basaveshwar Teaching and General Hospital, Gulbarga were selected for the study. The patients belonged to the age group of 20-30 years.

There were twenty males and seventeen females. Two patients received 100mg, 25 patients 200mg and 10 patients received 300mg of Dilantin Sodium (Parke Davis) capsule daily at night between 9-10pm.

The period of the exposure to the drug varied from 1-5 years. Ten healthy volunteers of same age group who were not receiving any drugs were the control for the study.

None of the subjects displayed any hepatic, renal, cardiovascular or other CNS disturbances when examined in the OPD.

10ml of blood was collected from each patient between 9-10am. 2ml of serum was extracted from each sample; serum phenytoin level was measured using UV Spectrophotometer, Bausch and Lomb 21 by the method of Dill.[4]

5ml of blood was collected to measure the following biochemical parameters:

- Serum AST
- Serum ALT
- Serum ALP

Instrument – Ciba Corning Blood gas 288 system and other biochemical parameters are measured by Technicon-RA-XT Auto Analyser.

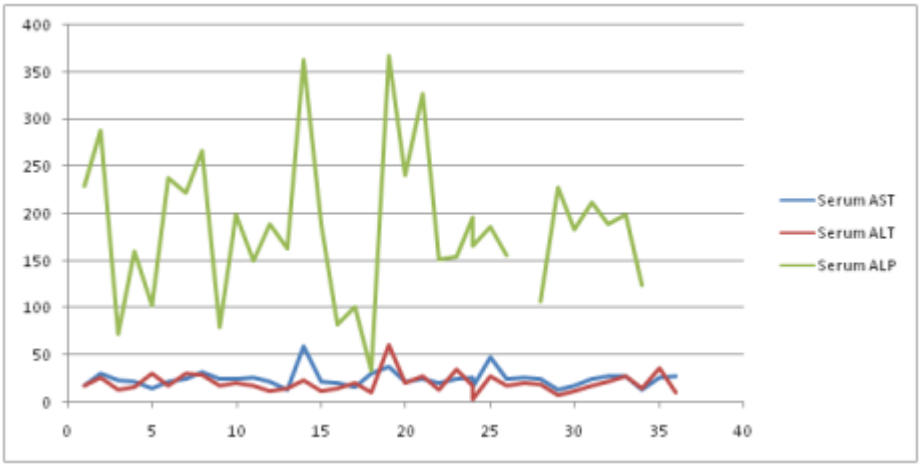
RESULTS: Serum phenytoin levels have been estimated in all 37 patients

Serum AST and ALT have been estimated in 37 patients while serum ALP levels were evaluated in 34 patients. The normal range of all values were recorded from Chandra Diagnostic Centre, Mangalore.

Sl. No.	Serum phenytoin (µg/ml)	Serum AST IU/L Normal Range upto 35 IU/L	Serum ALT IU/L Normal Range upto 40 IU/L	Serum ALP IU/L Normal Range upto 108-306 IU/L
1	11.42	18	17	230
2	18.57	30	26	289
3	13.9	23	13	73
4	22	21	16	161
5	10.6	15	31	103
6	13	21	17	239
7	14.5	25	31	223
8	22.3	32	29	267
9	16.5	24	17	80
10	26	24	21	200
11	10.4	26	17	151
12	13.6	22	12	189
13	11.75	13	15	164
14	18	59	23	363
15	11.6	22	12	189
16	26	20	15	83
17	20.5	16	21	101
18	15.4	30	10	34
19	10.7	38	61	368
20	29	21	20	241
21	19	25	28	328
22	19	20	13	152
23	17	24	35	155
24	11.75	26	17	197
25	20	16	3	167
26	14.3	47	28	187
27	16.4	25	17	156
28	7	26	20	--
29	7	25	19	108
30	8.2	13	8	229
31	8	18	12	184
32	10	24	17	212
33	9.3	27	22	190
34	4	27	28	199

35	10	13	14	125
36	8.23	26	36	--
37	4.23	28	10	--
Total	529.86	910	751	6347

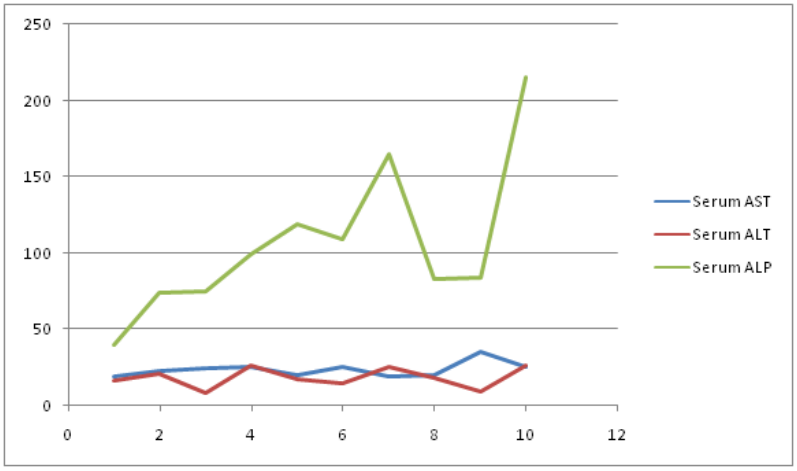
Table-1: Serum Phenytoin levels and biochemical parameters of (liver enzyme levels) of 37 epileptic patients



Graph 1

S. No.	Serum AST IU/L	Serum ALT IU/L	Serum ALP IU/L
1	19	16	40
2	23	21	74
3	24	8	75
4	25	26	99
5	20	17	119
6	25	14	109
7	19	25	165
8	20	18	83
9	35	9	84
10	25	26	215
Total	235	180	1063

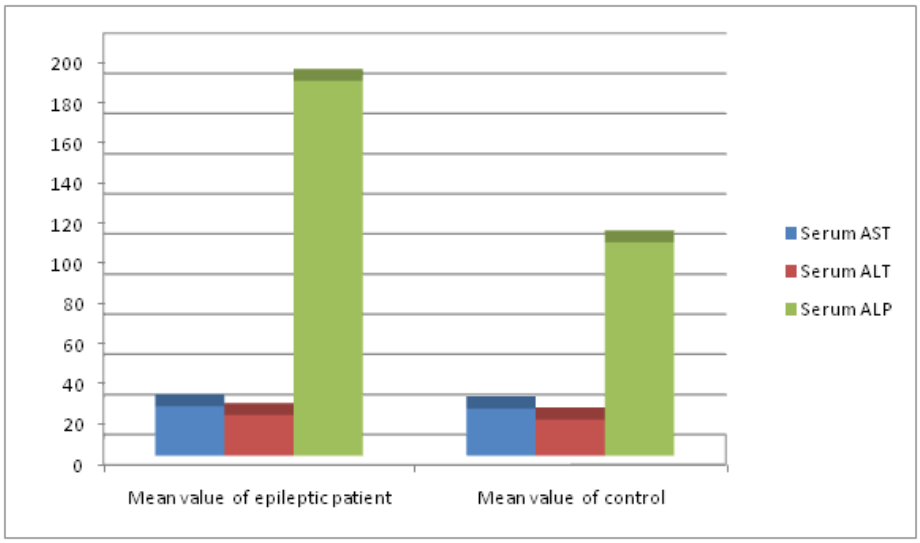
Table 2: Control group biochemical parameters



Graph 2

	Serum AST IU/L	Serum ALT IU/L	Serum ALP IU/L
Mean value of epileptic patient	24.59	20.29	186.67
SD of epileptic patient	8.87	10.34	78.11
Mean value of control	23.5	18	106.3
SD of control	4.76	6.56	50.49
SE	2.927	3.45	5.127
T test of	0.37	0.66	15.62
P	>0.05	> 0.05	< 0.001

Table 3: Comparison between biochemical parameters of epileptic patients receiving phenytoin sodium and biochemical parameters of control group



Graph 3

DISCUSSION: The present study has set its focus on estimating serum phenytoin levels and correlating these values with various biochemical parameters in a select group of patients suffering from grand-mal epilepsy. This has been done bearing in mind that these values have come under the influence of various factors which can alter the final reading. The study has not put its focus on finding out which is the best combination of drugs to be given in grand-mal epilepsy or its dosing pattern.

The results of the present study have arrived at the following findings of interest:

- Elevation of serum alkaline phosphatase (ALP) in the epileptic patients as compared to the control group. This finding is highly significant.
- Serum AST and ALT levels did not show any elevation.

Various other studies have shown elevated levels of serum ALP in patients receiving phenytoin sodium therapy.[5,6,7] This increase in serum ALP can be attributed to cholestasis induced by drug or as a consequence of hepatocellular toxicity.

Other possible mechanisms which can explain this elevation in serum ALP with phenytoin therapy are altered metabolism of vitamin D[8] and inhibition of intestinal absorption of calcium.[9]We should also remember that gross variation from the normal must be considered as a forerunner of or already confirmed hepatotoxicity.

CONCLUSION: The present study summarizes its findings in patients of grand-mal epilepsy receiving phenytoin therapy.

- Elevation of serum alkaline phosphatase levels in comparison to the control group.
- Other parameters such as serum aspartate transaminase and alanine transaminase were within normal limits and there was no significant correlation.

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AUTHORS:

1. Ashok Binjawadgi
2. Patil B.V.
3. Shrinivas Raikar
4. Manu Bhardwaj
5. Basavambika Anandi
6. Shivaraj

PARTICULARS OF CONTRIBUTORS:

1. Associate Professor, Department of Pharmacology, MR Medical College, Gulbarga.
2. Professor, Department of Pharmacology, MR Medical College, Gulbarga.
3. Post Graduate Resident, Department of Pharmacology, MR Medical College, Gulbarga.
4. CMO, Department of Pharmacology, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi.
5. Post Graduate Resident, Department of Pharmacology, MR Medical College, Gulbarga.
6. Post Graduate Resident, Department of Pharmacology, MR Medical College, Gulbarga.

NAME ADRRESS EMAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Ashok Binjawadgi,
Associate Professor,
Department of Pharmacology,
MR Medical College,
Gulbarga, Karnataka.
Email – ashok_binjawadgi@yahoo.com

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