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To Study the Effect of Antiepileptic Drugs on Serum Alkaline Phosphatase Levels in the Epileptic Patients

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ABSTRACT

Background: Epilepsy is treated with anti-epileptic drugs (AEDs) mainly in most of the patients. AEDs are to be initiated after having 2 seizures within a 6-month period. These have been observed to be associated with an increased frequency of hypocalcemia, hypophosphataemia, elevated serum alkaline phosphatase activity, reduced 25-hydroxy Vitamin-D concentrations, and decreased bone mass in patients receiving long term therapy. It is also observed that duration of AED therapy was the most important contributing factor for the alterations of these biochemical parameters. Objective: To study the effect of antiepileptic drugs on serum alkaline phosphatase levels in epileptic patients and to compare the relationship of change with duration of drug intake. Study Design: A Case Control Prospective Study. **Methods:** A total number of 100 subjects presenting with epilepsy in the OPD of Neurology department of Guru Nanak Dev Hospital, attached to Government Medical College Amritsar, were selected. **Results:** 50 epileptic patients taking Antiepileptic Drugs for more than 6 months constituted case group and 50 epileptic patients not taking Antiepileptic Drugs constituted control group. The study group patients were further divided according to duration of drug intake. **Conclusion:** AEDs causes significant increase in Alkaline phosphatase levels and this increase is further related to duration of drug intake.

Keywords: Alkaline Phosphatase, Epilepsy..

INTRODUCTION

Epilepsy is not a disease, but a syndrome of different cerebral disorders of the Central Nervous System (CNS) which is characterized by excessive discharges of large numbers of neurons.[1] Antiepileptic drug therapy is usually begun when the patient has suffered more than one unprovoked seizure within a year. Although the majority of treated patients will remain fully controlled, as many a 30% will continue to suffer seizures in the face of optimal deployment of antiepileptic medication.[2] Treatment of epilepsy is often a lifelong affair.[3] Anticonvulsant drugs are used in large quantities during long-term antiepileptic therapy and the treatment may be associated with various metabolic abnormalities in connective tissues, endocrine system and the liver. Anticonvulsants may alter liver function and increase the activity of hepatic microsomal enzyme system.[4] Generally, phenobarbital, phenytoin and carbamazepine are called as "enzyme inducing antiepileptic drugs" because of their activating effects on hepatic microsomal enzyme system.[5,6]

Various adverse effects, such as cerebral atrophy, peripheral neuropathy, metabolic bone diseases, hirsutism, coagulation defects, and a decrease in the level of folate and vitamin B12, can be seen with long-term antiepileptic therapy.[7] It can also alter liver function and increase the activity of the hepatic microsomal enzyme Overall,[8] third-generation AEDs were generally well tolerated with only mild-to-moderate side effects, and did not exhibit higher risk of serious adverse events.[9] In 2011, the new consensus criteria defined drug-induced liver injury as an increase in the alkaline phosphatase level of >2 times the upper limits of normal especially when associated with elevations in γ-glutamyl transpeptidase.[10]

Common AEDs used are Phenobarbitone, phenytoin, carbamazepine, sodium valproate etc. Keith G.Tolman and William Jubiz in their study in American Fork, Utah observed hypocalcaemia, hypophosphataemia, and raised serum alkaline phosphatase levels in epileptic patients on AEDs. They also observed that duration of AED therapy was the most important contributing factor for the alterations of these biochemical parameters.[11]

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MATERIALS AND METHODS

The present study was undertaken in the Department of Biochemistry, Government Medical College, Amritsar, in collaboration with Department of Neurology, Guru Nanak Dev Hospital, Amritsar. The study was approved by institutional ethics and thesis committee.

Suitable cases were selected from the patients attending O.P.D. of Neurology Department, Guru Nanak Dev Hospital, Amritsar.

Study design

This was a case control prospective study comprising a total of 100 subjects presenting with epilepsy in the O.P.D. of Neurology Department of Guru Nanak Dev Hospital, attached to Government Medical College, Amritsar.

Selection of cases

50 epileptic subjects taking Antiepileptic drugs for more than 6 months were considered as study group. These are again divided into two groups depending upon duration of treatment with AEDs taken i.e. Group - A (6-24 months) and Group – B (>24 months).

Selection of controls

50 epileptic subjects not taking Antiepileptic drugs were considered as control group.

Biochemical investigations were done in all Epileptic patients attending O.P.D. of Neurology Department, Guru Nanak Dev Hospital, Amritsar.

A standard proforma was employed in each case and detailed history regarding the disease was accurately recorded and investigations were done.

Written Informed consent was taken from the cases and controls included in the study.

Exclusion criteria

Patients suffering from following diseases were excluded from the study:

- Hyperparathyroidism
- Hypoparathyroidism
- Chronic renal failure
- Rickets
- Pregnant females
- Persons taking calcium supplement

Collection and processing of blood samples

5 ml of venous blood was taken from all subjects after 12hour overnight fast in a dry disposable syringe under all aseptic precautions by venepuncture in the anticubital vein in a sterile, dry acid washed vial for biochemical analysis.

Preparation of serum

The blood was allowed to stand for half an hour. After clot formation, the supernatant was centrifuged. All the samples were processed for serum alkaline phosphatase

Biochemical assay of Serum Alkaline Phosphatase

Serum Alkaline Phosphatase was estimated by using King and Kings method

Principle

Phenol was released by enzymatic hydrolysis from disodium-phenyl-phosphate under defined conditions of temperature, time and pH..This reacted with 4-aminoantipyrine in the presence of alkaline oxidizing agent to give a red coloured compound which was estimated at 520nm at against a reagent blank.

Reagents

1. Buffer Substrate.
2. Phenol Standard
3. Coloured Reagent

Buffer substrate was available in powdered form so it was always prepared freshly by adding 4.5ml of distilled water to the available vial.

Procedure

Taken 4 test tubes and labeled them as – Test [T], Standard [S], Control [C], and Blank [B].

Sr. No.	Reagents	T	S	C	B
1	Buffered Substrate	1ml	1ml	1ml	1ml
2	Distilled water	1ml	1ml	1ml	1ml
Incubate at 37oc for 3mns.					
3	Serum	0.1ml			
4	Phenol Standard		0.1ml		
Incubate at 37c for 15mns.					
5	Serum			0.1ml	
6	Coloured Reagent	2ml	2ml	2ml	2ml

Mixed well and measured the absorbance at 510nm against distilled water.

Serum Alkaline Phosphatase:

O.D of T-O.D of C X 10

O.D of S-O.D of B

Normal Alkaline Phosphatase levels = 3-13 KA/dl

RESULTS

The present study was undertaken with an aim to study effect of antiepileptic drugs on serum levels of calcium, phosphorous and alkaline phosphatase. For this, a total number of 100 epileptic subjects were selected, out of which 50 epileptic subjects taking Antiepileptic drugs for more than 6 months constituted case group and 50 epileptic subjects not taking any Antiepileptic drugs constituted control group. The cases and controls were selected from the O.P.D. of Neurology Department, Guru Nanak Dev Hospital, Amritsar. The serum samples of both the groups were subjected to biochemical investigations of serum alkaline phosphatase. The subjects were divided into two groups:

Group I - Epileptic patients not on AEDs.

Group II - Epileptic patients on AEDs. for more than 6 months.

Group II - again divided into two groups depending on duration of treatment with AEDs taken i.e. Group - A and Group - B

Table 1: Distribution of Cases According To Duration Ofanti-Epileptic Drugs Taken

Group	Duration of treatment	No. of cases	Percentage
A	6 - 24 months	14	28
B	>24 months	36	72

[Table 1] indicates that the cases were divided into two groups according to duration of treatment i.e. Group A and Group B.

Group A included cases having duration of treatment between 6-24 months (n=14) i.e. 28%. Group B included cases having duration of treatment between > 24 months (n=36) i.e. 72%.

Table 2: Variations in Serum Alkaline Phosphatase Concentration in Epileptic Patients with and Without Treatment

Epileptic patients (N=100)	Serum Alkaline Phosphatase (KA/dl)	
	Range	Mean+S.D.
Without Treatment n=50 (Group I)	5.2-13	10.6760+2.34
With treatment n=50 (Group II)	16-118	63.0680+34.74
Test Applied t-test	t=10.64	P<0.001

[Table 2] indicates variations in serum - alkaline phosphatase concentration in epileptic patients with and without treatment. Group-I comprised of epileptic patients without treatment and Group- II comprised of epileptic patients with treatment.

Serum alkaline phosphatase levels in Group -I patients ranged from 5.2-13 with Mean+S.D. 10.6760+2.34. In Group- II patients serum alkaline phosphatase levels ranged from 16-118 with Mean + S.D. 63.0680 + 34.74. A highly significant increase ($p< 0.01$) in serum alkaline phosphatase levels were observed in Group- II patients as compared to Group I patients.

Hence alkaline phosphatase altered highly significantly in Group-II patients as compared to

Group I patients

Table 3: variations in alkaline phosphatase concentration in epileptic patients taking aeds i.e. In group ii patients according to duration of treatment

Group	Total No.	Serum alkaline phosphatase (ka/dl)	
		Range	Mean+S.D.
A (6-24 months)	14	13-118	28.79+12.86
B (>24 months)	36	16.6-122	76.40+31.23

(t =5.49; p<0.01)

[Table 3] indicates variations in Alkaline phosphatase concentration in epileptic patients taking AEDs i.e. in Group II patients according to duration of treatment i.e. in two duration groups Group A and Group B

In duration Group A i.e. 6-24 months, serum Alkaline phosphatase levels ranged from 13-118 with Mean+S.D. 28.79+12.86. In duration Group B i.e. >24 months serum Alkaline phosphatase levels ranged from 16.6-122 with Mean+S.D.76.40+31.23

The above table shows that serum Alkaline phosphatase levels rises significantly ($p<0.01$) in patients taking AEDs and this increase in serum Alkaline phosphatase levels again depend on duration of treatment levels. More the duration of treatment with AEDs, more is the rise in Alkaline phosphatase levels.

DISCUSSION

Epilepsy is one of the most common neurological diseases. It is estimated that approximately 50 million people worldwide suffer from epilepsy. The most common treatment of epilepsy is based on long-term use of antiepileptic drugs (AEDs). The frequency of the most common antiepileptic drugs is rare but the consequences can be very serious leading to death or liver transplantation due to acute liver failure induced by these drugs.[12]

AEDs may cause various side effects like metabolic, biochemical, and radiological abnormalities.[13-15] The severity of bone and biochemical abnormalities is thought to correlate with the duration of AED exposure and the number of AEDs used. . In the present study, effect of anti-epileptic drugs in epileptic patients has been investigated.

In the present study, variations in serum alkaline phosphatase levels were studied in both Group I epileptic patients i.e. not on any AEDs and Group II epileptic patients i.e. taking AEDs for more than 6-mths the mean serum alkaline phosphatase levels in Group I patients II patients were 63.07+34.74. The increase in serum alkaline phosphatase levels in Group II patients was highly significant ($p < 0.001$) [Table 2]. Weinstein RS, Bryce GF, Sappington LJ, King DW, and Gallagher BB also observed raised serum alkaline phosphatase levels in epileptic patients on AEDs in their study conducted on outpatients with epilepsy at New Jersey in 1984.[16] Similar findings were also observed in other studies conducted by Richens A. and Rowe DFJ in 1970,[17] Hahn TJ, Hendin BA and Scharp CR in 1972,[18] Bouillon R, Reynaert J Moor PD, Claes JH in 1975,19Hoikka V, Repo A and Savolainen K in 1981,[20] and O'Hare JA, Duggan B, Driscoll D and Callaghan N. in 1980.[21]

In the present study, Group II patients were also divided according to duration of therapy into two groups i.e. Group A (6-24 months) and Group B (> 24 months).

Group A include 28% patients where as Group B include 72% patients [Table 1]. Also variation in

serum alkaline phosphatase levels were studied in both the Groups and it had been found that serum alkaline phosphatase levels were increased in both the groups but group B shows more increased levels as compared to group A [Table 3] The hepatoxicity induced by antiepileptic drug occurs because of production of reactive toxic metabolite/s or because of induction of immunoallergic reactions.[22,23]

Hence more is the duration of therapy, more is the variation in serum alkaline phosphatase levels were observed. Similar findings were reported by Andress DL, Ozuna J, Tirschwell D, Grande L, Johnson M, Jacobson AF, et al. in 2002.[24]

CONCLUSION

The present study reveals that patients on AEDs show biochemical changes i.e. increase in serum Alkaline phosphatase levels. This change is more pronounced if AEDs are taken for longer duration.

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