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Estimation of Serum Levels of Alanine Transaminase, Aspartate Transaminase, Alkaline Phosphatase in Donepezil Therapy of Alzheimer's Patients in a Tertiary Care Hospital

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ABSTRACT

Neurodegenerative diseases are incurable and debilitating conditions that result in progressive degeneration and/or death of nerve cells. This causes problems with movement (called ataxis), or mental functioning (called dementia). Alzheimer's is a chronic neurodegenerative disease of the brain that causes problems with memory, thinking and behavior. It is not a normal part of aging. The cause of Alzheimer's disease is poorly understood. The risk factors include a history of head injuries, depression or hypertension. The medications used to treat Alzheimer's disease are acetyl cholinesterase inhibitors and NMDA receptor antagonists. Donepezil is a cholinesterase inhibitor. It works by increasing the amount of acetylcholine in the brain, which may help to reduce the symptoms of dementia in patients with Alzheimer's disease. The administration of Donepezil causes marked elevation in the serum liver enzymes like alanine transaminase, aspartate transaminase, alkaline phosphates.

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INTRODUCTION

Alzheimer's is a type of dementia that causes problems with memory, thinking, and behavior. Symptoms usually develop slowly and get worse over time becoming severe enough to interfere with daily tasks. Alzheimer's disease accounts for 60-80 percent of dementia cases. Alzheimer's is not a normal part of aging, although the greatest known risk factor is increasing age and the majority of people with Alzheimer's are 65 and older [1]. The most common early symptom of Alzheimer's is difficulty in remembering newly learned information. Because Alzheimer's changes typically begin in the part of brain that affects learning. As Alzheimer's advances through the brain it leads to increasingly severe symptoms, including disorientation, mood and behavior changes, deepening confusion about events, time and places; unfounded suspicions about family, friends, and professional caregivers; more serious memory loss and behavior changes; and difficulty speaking, swallowing and walking [2].

- There are two types of medications used to treat Alzheimer's disease:

Acetyl cholinesterase inhibitors and NMDA receptor antagonists.

Cholinesterase inhibitors are a type of drug that boosts the amount of acetylcholine available to nerve cells by preventing its breakdown in the brain. The generic names for the cholinesterase inhibitors are donepezil, rivastigmine and galantamine.

- Donepezil was originally patented as the brand name Aricept, but is more widely available now as just generic Donepezil [3].

The NMDA receptor antagonist is memantine. It was originally patented as Ebixa and is now also available as generic memantine. Other UK brand names for memantine include Maruxa and Nemdatine. Donepezil is used to treat confusion (dementia) related to Alzheimer's Disease. It does not cure Alzheimer's disease, but it may improve memory, awareness, and the ability to function. This medication is an enzyme blocker that works by restoring the balance of natural substance (neurotransmitter) in the brain [4].

Alzheimer disease is associated with a cholinergic deficiency in the cerebral cortex, and the increase in concentration of acetylcholine with acetyl cholinesterase inhibition is associated with improvement in cognitive function in patients with Alzheimer dementia. Donepezil has

selective activity for acetyl cholinesterase in the central nervous system with little effect on the enzyme in peripheral tissue. Donepezil was approved for use in the United States in 1996 and is currently the most commonly used acetyl cholinesterase inhibitor used for management of Alzheimer disease. Donepezil is available as regular tablets of 5 and 10 (and recently 23 mg) and as orally disintegrating tablets of 5 and 10 mg in generic forms and under the brand name Aricept. Donepezil is also available as a solution of 1 mg/mL for oral administration. The usual maintenance dosage is 5 to 10 mg once daily. Patients who tolerate the 10 mg daily dose may benefit from a higher dose of 23 mg daily [5]. Common side effects include diarrhea, nausea, vomiting, dizziness, fatigue, insomnia, vivid dreams, anxiety, restlessness, blurred vision, dry mouth and pruritus, symptoms common to cholinergic stimulation. Donepezil binds and inactivates reversibly the cholinesterase, thus inhibiting hydrolysis of acetylcholine. This results in increased acetylcholine concentrations at cholinergic synapses [6].

Donepezil marketed under the trade name Aricept is a medication used in the palliative treatment of Alzheimer's disease. Donepezil is used to improve cognition and behavior of people with Alzheimer's but does not slow the progression of or cure the disease [7].

Donepezil binds and reversibly inactivates the cholinesterases, thus inhibiting hydrolysis of acetylcholine. This results in an increased acetylcholine concentrations at cholinergic synapses [8].

MATERIALS AND METHODS

Study Design: A prospective experimental study.

Study Population: Patient diagnosed with Alzheimer's.

Study Setting: Neurology Department Pushpagiri Medical College Hospital, Thiruvalla.

IEC NO: PCP/E3/01A/14/2016

Study Period: 6 months

Sample Size:

60 patients diagnosed with Alzheimer's disease.

$N = (Z^2_{1-\alpha/2})\ (1-p)\ p$ where p: Expected proportion

$\zeta^2\ p$ ζ: Relative precision

$1-\alpha/2$: Desired confidence level

Inclusion Criteria

- Alzheimer's patients receiving donepezil.
- IP/OP patients.
- Both male and female patients.
- Capable of reading and writing English and Malayalam.
- Patients above 30 years.

Exclusion Criteria

- Patients who are not willing to participate.
- Avoid patients having diseases like chronic liver disease, Alcoholic liver disease, Cirrhosis, Hepatitis etc.

Brief Procedure

A prospective, paired, follow up, an experimental study was conducted on the topic, to estimate the liver function on donepezil therapy in Alzheimer's patients. Informed consent of the patients taken before the study. Patients data collection form were taken to record the demographic details of the patients. It was 6 month study, where 60 patients will be included and one month follow up will also be used. For the estimation of ALT, AST, ALP, serum was collected from the laboratory of Pushpagiri Medical College Hospital and determined by using semi auto analyzer and colorimetry in the Pushpagiri College of Pharmacy. All the patients should be aware of brief introduction of the study. Informations regarding demographic details of the patient, etiology, past medication history, current medications,

drug administration, comorbidities, were noted. Morisky Medication Adherence Scale - 4 was used to determine medication adherence.

Determination of Aspartate Transaminase

Procedure

Wave length - 340

Temperature – 37^0c

Read against reagent blank

Reagent 1 - 240µL

Sample - 30µL

Mix and wait 4 minutes and 43 seconds then add.

Reagent 2 - 60µL

Mix and after a second incubation, measure the change in absorbance per minute [ΔA/min] during 159 seconds.

Determination of Alkaline Phosphatase

Wave length – 405nm

Temperature – 37^0c

Procedure

Pipette into Test tubes

SAMPLE - 20µl

REAGENT - 1000µl

Mix well and incubate at 37^0c for 60 sec. Measure absorbance increases every 30 sec for 2 min and determines the ΔA/min.

Determination of Alanine Transaminase

Procedure

Working reagent

Mix 1 volume of R2 substrate with 4 volume of R1 buffer.

Stability 21 days at 2-8^{0}c or 72 hrs at room temperature (15-25^{0}c).

- Adjust the instrument to zero with distilled water.
- pipette into a cuvette
- Working reagent (mL) – 1.0
- Sample (mL) – 100
- Mix and incubate for 1 min
- Read the absorbance (A) of the sample, start the stopwatch and read the absorbance at 1 min interval thereafter for 3 min.
- Calculate the difference of absorbance and the average absorbance difference per minute (ΔA/min).

RESULTS AND DISCUSSION

- **Age**

The study population belongs to 40-80 years age group and the mean age is 68.28 years. Most of the study populations with increased age of 71-80 are more prone to Alzheimer's disease.

- **Gender**

In this study, most of the Alzheimer's patients were male (70 %) followed by females (30 %). Thus disease increases with male gender.

- **Family History**

66.7% are having family history of disease and 33.3% does not show any family history. Thus most of the Alzheimer's patients were having family history.

- **Neuropsychiatric Comorbidities**

46.7% shows no neuropsychiatric comorbidities, 30% patients show loss of sensation, 6.7% shows depression and 16.7% irritation.

- **Etiology**

Out of total population, aging increases the chance of disease commonly (51.7% in this study). Others like Genetic with 26.7%, dementia with 5%, obesity 13.3% and head injury with 3.3% respectively.

- **Medication Adherence**

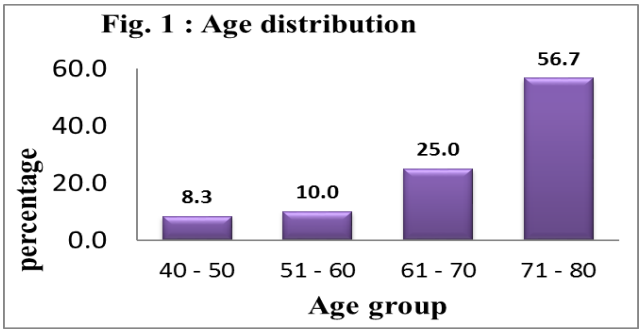
Before medication administration most of the patients were medium adhered to drug after treatment it increases to high adherence with pharmacist intervention.

- **Effect of Donepezil on Serum AST, ALT, ALP Level**

Since P<0.001 the mean level AST (39.47 to 53.93) was significantly increased after one month.

Since P<0.001 the mean level ALT (46.83 to 59.47) was significantly increased after one month.

Since P<0.001 the mean ALP (91.73 to 113.43) level was increased significantly after one month.



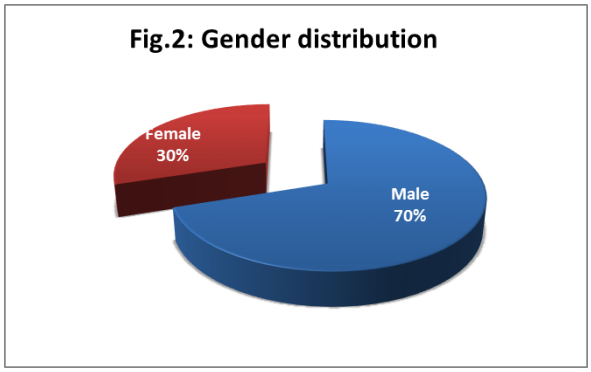


Fig.2: Gender distribution
Female
30%
Male
70%

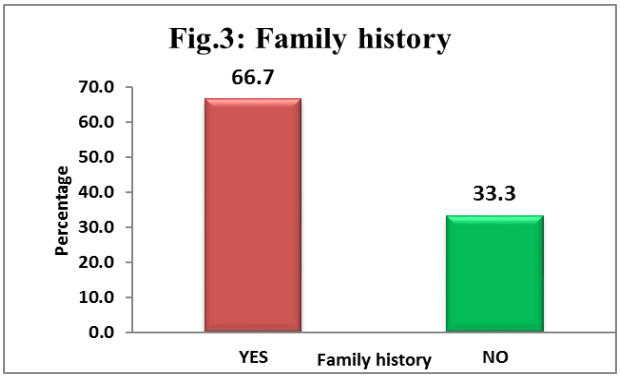


Fig.3: Family history
66.7
33.3
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
Percentage
YES
Family history
NO

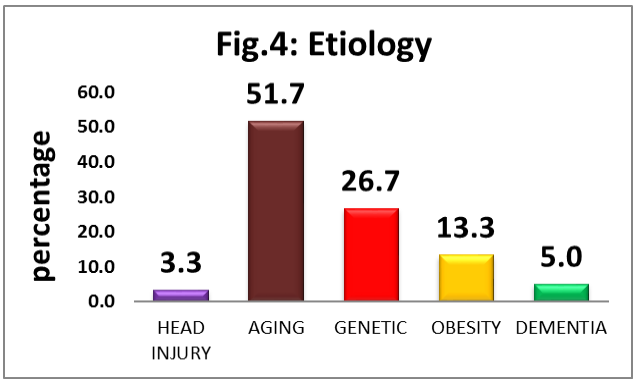


Fig.4: Etiology
60.0
50.0
40.0
30.0
20.0
10.0
0.0
percentage
3.3
51.7
26.7
13.3
5.0
HEAD INJURY
AGING
GENETIC
OBESITY
DEMENTIA

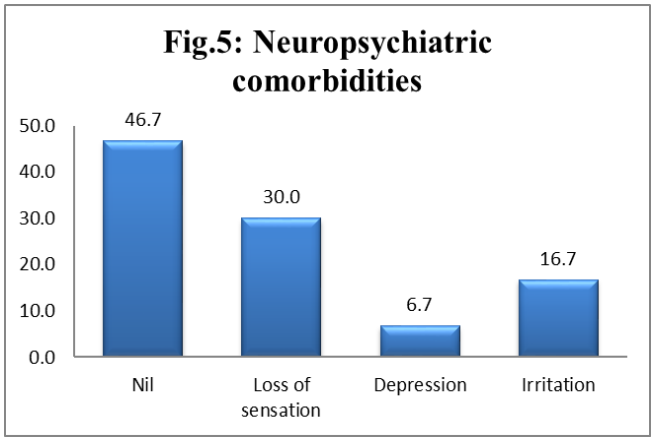
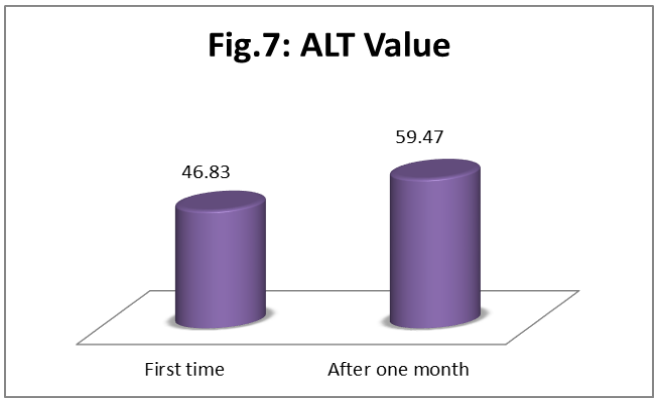
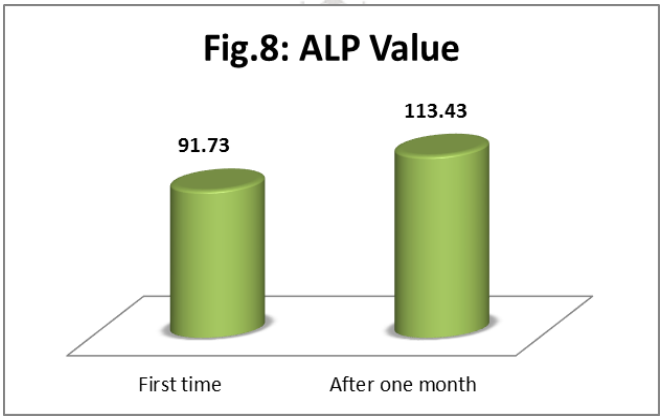


Fig.5: Neuropsychiatric comorbidities
50.0
40.0
30.0
20.0
10.0
0.0
46.7
30.0
6.7
16.7
Nil
Loss of sensation
Depression
Irritation





CONCLUSION

The studies regarding the effect of drug Donepezil on liver enzymes are of much importance and are very rare. It is important to monitor liver function test while taking Donepezil. The study will be very informative to the patients and medical practitioner. The study on Estimation of serum levels alanine transaminase, aspartate transaminase, alkaline phosphatase in donepezil therapy of Alzheimer's patients in a tertiary care hospital was done to ensure whether liver enzymes increased with drug administration along with predisposing factors and medication adherence. The drug selected is donepezil and its effect on serum

AST, ALT, ALP level was determined. Since P<0.001 the mean level AST, ALT and ALP level was significantly increased after one month. On evaluating predisposing factors it observed that Alzheimer's disease increase with advancing age, genetic factor and predominant in males compared to females. Among etiology mostly in dementia condition AST, ALT, ALP found to increase after treatment. Most of the patients show no much side effects. But commonly observed side effect is dyspepsia (13.3%). Before medication administration most of the patients were medium adhered to drug after treatment it increases to high adherence with pharmacist intervention.

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