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A STUDY ON THE EFFICACY ANDTOLERABILITY OF PENTOXIFYLLINE IN ALCOHOLIC HEPATITIS

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ABSTRACT

OBJECTIVE: To evaluate the efficacy and tolerability of pentoxifylline at the dose of 400mg thrice a day in patients with alcoholic hepatitis. METHODOLOGY: This open, prospective, non comparative study was conducted in 50 male patients between 20-50 years of age with alcoholic hepatitis attending Department of Hepatology, Madras Medical College & Rajiv Gandhi Govt. General Hospital, Chennai between September 2008 – March 2009. They were treated with pentoxifylline 400mg thrice daily for a period of 6 weeks. Assessments were done at baseline, after 3 weeks and 6weeks for liver function test (aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase, gamma glutamyltransferase, bilirubin, prothrombin time, serum proteins, International Normalised Ratio (INR) and complete blood count (CBC). RESULTS: Out of 50 patients included, 49 patients completed the study and one patient withdrew due to transfer of occupation. There were significant reduction in the AST, ALT, AST/ALT ratio, bilirubin (0.001) at the end of 3rd and 6th weeks. There was also significant increase in A/G ratio by 31.92% (P=0.02) and reduction in GGT by 61.51%, prothrombin time by 21.54% and INR by 18.85% from baseline (p=0.001). CONCLUSION :Pentoxifylline has resulted in a high improvement in all the laboratory parameters due to the anti-inflammatory action with lack of adverse reactions in patients with alcoholic hepatitis suggesting that pentoxifylline could be a potential first line pharmacotherapy in alcoholic hepatitis patients.

1.0 INTRODUCTION

Alcoholic hepatitis is a syndrome of progressive inflammatory liver injury associated with long-term heavy intake of ethanol and is a major cause of morbidity and mortality worldwide.[1] It is an acute or acute on chronic hepatic inflammatory response syndrome which is part of the spectrum of diseases that result from alcohol induced liver injury, ranging from the most common asymptomatic fatty liver to fulminant hepatitis and cirrhosis in the long term. Although, it is difficult to predict the clinical response in an individual patient, as only a minority of individuals consuming large amounts of alcohol develop alcoholic hepatitis,[2] The threshold for developing alcoholic liver disease in men is an intake of 60 to 80 g/day of alcohol for 10 years, while women are at increased risk for developing similar degrees of liver injury by consuming 20–40 g/day.[3]

Although corticosteroids are commonly used for the acute alcoholic hepatitis, a 2008 Cochrane review of 15 randomized controlled trials with a total of 721 patients concluded that glucocorticoids did not statistically reduce mortality compared with placebo.[4] This review suggested mortality benefit only when the patients have hepatic encephalopathy or have a Maddrey discriminant function (DF= 4.6 x [prothrombin time control (seconds)] + serum bilirubin (mg/dL) above 32. Also, glucocorticoids are not free of adverse effects and has had its share of controversies.[5]

Pentoxifylline, a non specific phosphodiesterase inhibitor has been reported to benefit in patients with alcoholic hepatitis.[6]Pentoxifylline is known to benefit through mechanisms such as inhibition of phosphodiesterases, increased cAMP levels and downregulation of TNF-alfa, IL-1, IL-6, transforming growth factor beta (TGF –beta), interferon gamma (IFN-gamma), stellate cell activation and procollagen –I mRNA expression.[7]

This Prospective study was done to evaluate the efficacy and tolerability of pentoxifylline at the dose of 400mg thrice a day in patients with alcoholic hepatitis.

2.2 STUDY DESIGN

This Open label, Non comparative, Interventional, Prospective study was conducted at the Department of Pharmacology and Department of Hepatology, Madras Medical College and Govt. General Hospital, Chennai, India. The study was carried out from September 2008 – March 2009 for 6 weeks per patient. Patients attending Outpatient Department of Hepatology with alcoholic hepatitis were the study population. Total number of patients was 50.

2.3 SELECTION CRITERIA

2.3.1 INCLUSION CRITERIA:

- Age - 20-50 years, Sex - both genders
- Chronic alcoholics - 60-80 g/d in male, 20-40 g/d in female for 10 years with abnormal Liver Function Test
    - Elevated AST, ALT (80 to 120 IU/L), AST / ALT > 1
    - Elevated alkaline phosphatase (2-3 times of normal)
    - Elevated Bilirubin (3-5 mg/dl)
    - Elevated Prothrombin time (2 times of normal)
    - Total proteins (5-7 g/dl) or serum albumin < 3.5 g/dl
    - Polymorphonuclearleucocytosis> 70%

2.3.2 EXCLUSION CRITERIA:

- Patients with history ofnonalcoholic liver disease, advanced alcoholic cirrhosis, active GI bleeding, sepsis, tuberculosis, & other bacterialinfections
- Patients diagnosed with hepatocellular carcinoma, diabetes /hypertension / any chronic systemic illnesses

2.4 STUDY PROCEDURE

The study was conducted after getting approval from the Institutional Ethical Committee (No.16328). Out of 156 patients screened, 50 patients who fulfilled the inclusion and exclusion criteria were enrolled in the study after obtaining written informed consent.

2.5 TREATMENT PLAN

All patients received pentoxifylline at a dose of 400 mg thrice daily orally for a period of 6 weeks. Patients were dispensed drugs every week and were asked to return the empty containers at each visit to ensure compliance to therapy. Laboratory and clinical evaluations were done after 3 and 6 weeks. The assessment parameters were total WBC, polymorphs, lymphocytes, eosinophils, serum AST, ALT, alkaline phosphatase, serum bilirubin (total and direct), serum proteins, A/G ratio, GGT, prothrombin time, international normalized ratio (INR).

2.6 STATISTICAL ANALYSIS

Efficacy analysis were done as per protocol i.e. per-protocol (PP) population, whereas safety analysis were done on intent-to-treat (ITT) population of 50 patients. Overall comparison of laboratory values is done using One Way ANOVA and individual comparisons of baseline values with 3 and 6 weeks are done using paired 't' test.

3.0 RESULTS : TABLE 1: TC and DC

Laboratory parameters	Baseline Mean(S.D)	Week3 Mean(S.D)	Week6 Mean(S.D)	'p' (ANOVA)	'p'(vs 3wks)	'p'(vs 6wks)
Total WBC count	9362.0 (1365.0)	8988.0 (748.51)	8862.0 (766.89)	0.001	0.004	0.003
Polymorphs(%)	69.82(7.1)	63.30(3.9)	61.68(3.1)	0.001	0.001	0.001
Lymphocytes(%)	27.12(6.8)	33.86(4.1)	35.48(3.74)	0.001	0.001	0.001
Eosinophils(%)	2.88(2.2)	2.84(2.1)	2.84(2.1)	0.65	0.53	0.53

Figure 1: Change from baseline (%) in TC and DC

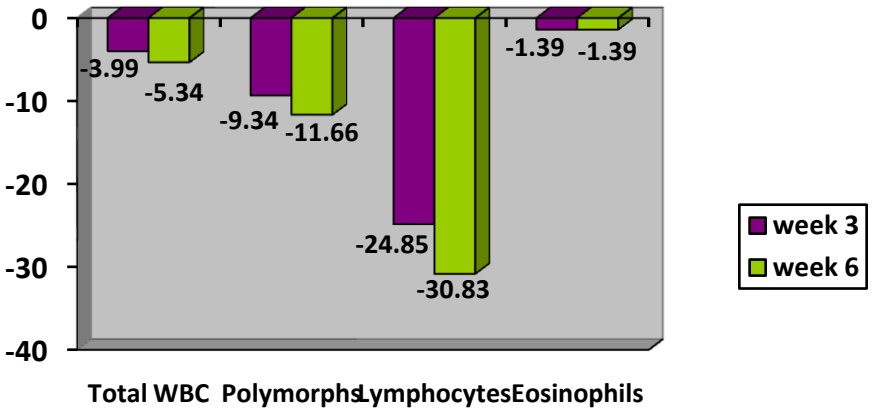


TABLE 2: LIVER ENZYMES

Laboratory parameters	Baseline Mean(S.D)	Week3 Mean(S.D)	Week6 Mean(S.D)	'p' (ANOVA)	'p'(vs 3wks)	'p'(vs 6wks)
AST(IU/L)	87.04(33.1)	49.64(17.9)	31.10(6.4)	0.001	0.001	0.001
ALT(IU/L)	60.52(18.4)	41.72(14.1)	28.72(5.9)	0.001	0.001	0.001
AST/ALT(IU/L)	1.39(0.3)	1.19(0.2)	1.07(0.1)	0.001	0.001	0.001
Alkaline phosphatase(IU/L)	223.18 (73.4)	153.70 (41.7)	103.60 (15.2)	0.001	0.001	0.001

Figure :2 Change from baseline (%) in liver enzymes

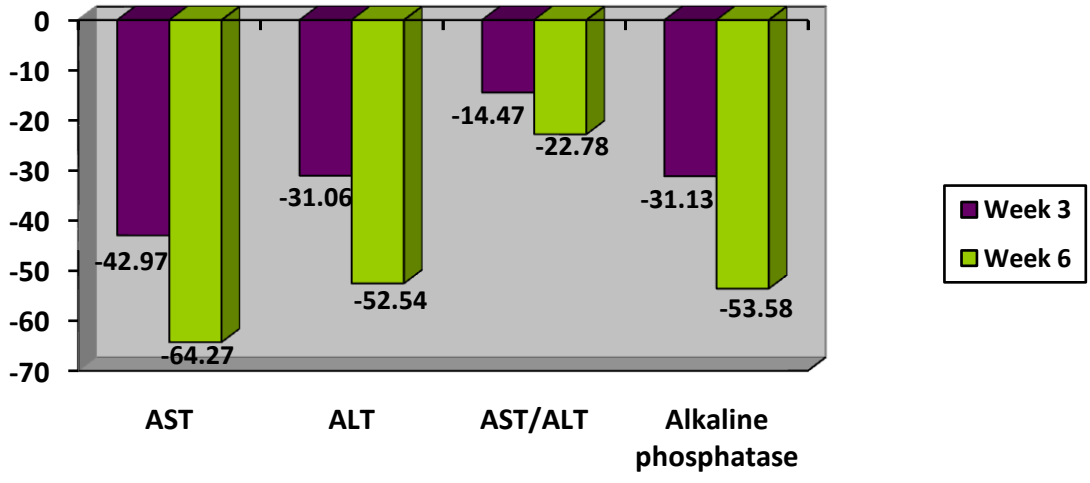


TABLE 3 : BILIRUBIN and PROTEINS

Laboratory parameters	Baseline Mean(S.D)	Week3 Mean(S.D)	Week6 Mean(S.D)	'p' (ANOVA)	'p'(vs 3wks)	'p'(vs 6wks)
Total bilirubin(mg/dl)	3.10(1.90)	1.70(1.0)	0.94(0.2)	0.001	0.001	0.001
Direct bilirubin(mg/dl)	1.63(0.9)	0.86(0.5)	0.46(0.3)	0.001	0.001	0.001
Total proteins(g/dl)	6.10(0.7)	6.63(0.4)	6.98(0.3)	0.001	0.001	0.001
Albumin(g/dl)	2.96(0.7)	3.57(0.5)	3.89(0.3)	0.65	0.53	0.53
A/G Ratio	0.95(0.3)	1.18(0.3)	1.25(0.2)	0.001	0.001	0.02

Figure 3: Change from baseline (%) in bilirubin and serum proteins

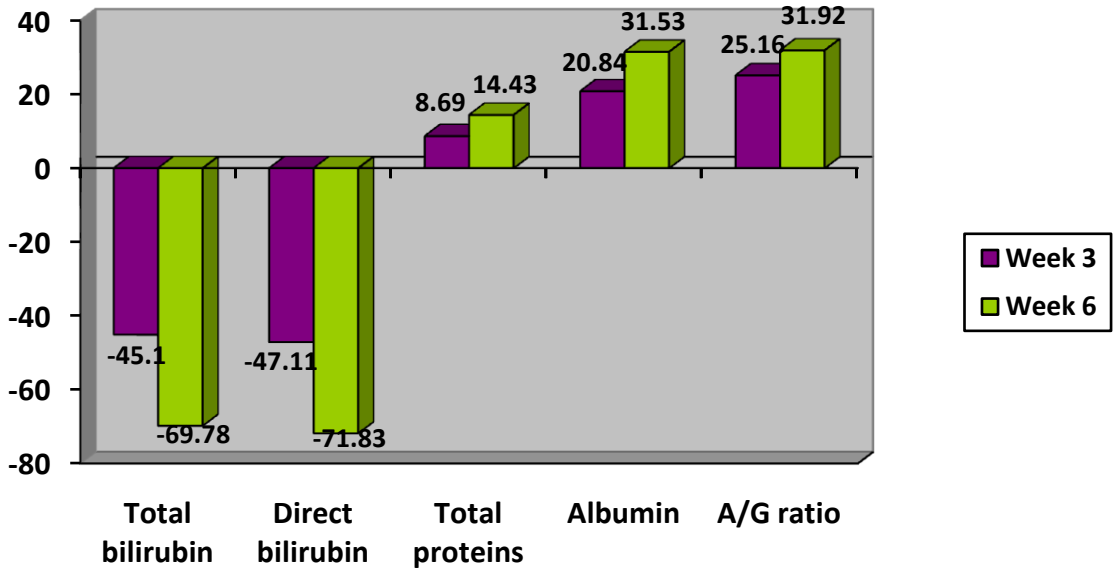
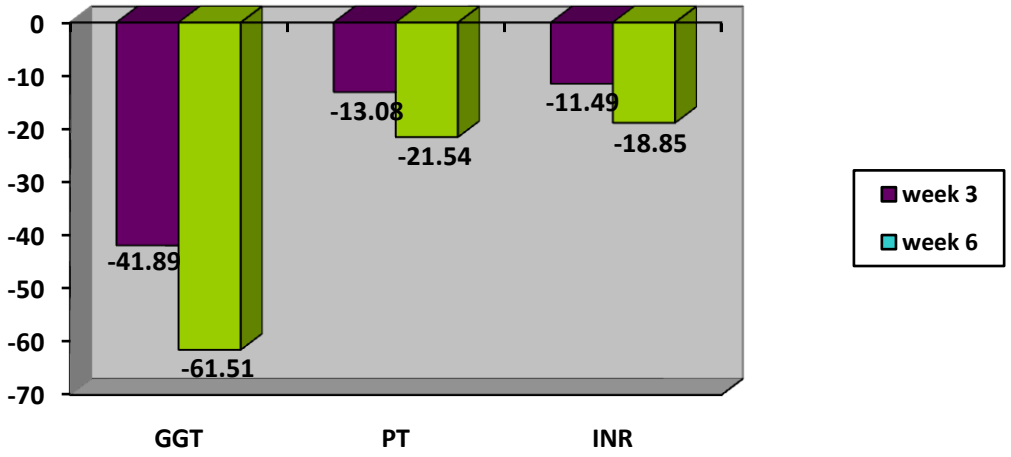


TABLE 4: GGT,PT, INR

Laboratory parameters	Baseline Mean(S.D)	Week3 Mean(S.D)	Week6 Mean(S.D)	'p' (ANOVA)	'p'(vs 3wks)	'p'(vs 6wks)
GGT(IU/L)	108.08(40.1)	62.80(33.3)	41.60(15.2)	0.001	0.001	0.001
Prothrombin time(sec)	18.10(3.5)	15.73(2.4)	14.20(1.4)	0.001	0.001	0.001
INR	1.59(0.3)	1.41(0.2)	1.29(0.2)	0.001	0.001	0.001

Figure 4: Change from baseline (%) in GGT, PT, INR



DISCUSSION

This study was conducted to evaluate the efficacy and tolerability of pentoxifylline in alcoholic hepatitis. In alcoholic hepatitis, inflammatory cytokines (TNF, IL-1, IL-8) have been postulated to play a significant role in the liver injury[8].Hence drugs that inhibit inflammatory cytokines form an important therapeutic approach in addition to alcohol cessation. It is hypothesized that pentoxifyllinehas shownanti inflammatory property and thereby it improves the liver functions and prevents the progression of alcoholic hepatitis to liver cirrhosis. In this study, pentoxifylline treated patients showed reduction in AST by 64.27%, ALT by 52.54%, AST/ALT ratio by 22.78%, alkaline phosphatase by 53.58%, total bilirubin by 69.78%, direct bilirubin by 71.83% at the end of 6 weeks from baseline with significant 'p' value of 0.001. There was also significant increase in total proteins by 14.43%, and albumin by 31.53% (p=0.001), A/G ratio by 31.92% p=0.02), reduction in GGT by 61.51%, reduction in prothrombin time by 21.54% and INR by 18.85% (p=0.001) from baseline at the end of 6 weeks. This study showed significant reduction in TC (p = 0.003) and DC (p = 0.001) from baseline. There were no adverse effects reported by any of the patients in our study group. Although earlier reports[12,13,14]recommend the potential use of pentoxifylline in patients with severe alcoholic hepatitis, this is probably the only study which reports the findings of pentoxifylline in patients with mild to moderate alcoholic hepatitis. Also, as in the present study, neither of the earlier studies reported improvement in GGT, which is an important laboratory tool for hepatic function assessment particularly in chronic hepatitis.

CONCLUSION

In this study, a high improvement in all the laboratory parameters and lack of adverse reactions withpentoxifylline in patients with alcoholic hepatitis suggest that pentoxifylline could be a potential first line pharmacotherapy for alcoholic hepatitis.

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