APRI index changes after 4 weeks treatment of Pentoxifylline in Chronic Hepatitis B

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ABSTRACT *Nowadays studies have shown that liver fibrosis is a reversible process. Theraupetic target on hepatic stellate cell (HSC) through inhibition of fibrotic signaling transduction is one of the way to treat liver fibrosis (e.g. pentoxifylline). APRI index, one of the indirect marker of liver fibrosis, had shown significant correlation (Spearman correlation $\gamma = 0.7$) with liver fibrosis degree in hepatitis B and C. This study was aimed to evaluate the effect of pentoxifylline treatment in 4 weeks for liver fibrosis measured by APRI index. We conducted clinical trial on eleven chronic hepatitis B patients from Adam Malik Hospital Medan, with positive HBsAg at least 6 months after follow up. They were treated with pentoxifylline for 4 weeks. Before and after treatment, APRI index was measured. The result showed a decrease of ALT (64.64±49.61 vs 50.64±26.13; p=0.28), but AST and APRI index increased (91.82± 100.16 vs 97.91±146.75; p=0.79) and (1.17±1.07 vs 1.31±1.84; p=0.96) respectively. It was concluded that the effect of pentoxifylline as antifibrotic in the liver measured by APRI index was not proven. It was shown that APRI index increased after 4 weeks treatment of pentoxifylline.*

Chronic hepatitis B is an important health issue in the world. Approximately 2 billion people in the world has been exposed to hepatitis B virus and about 400 million of them had suffered from chronic hepatitis B (Lok & McMahon, 2007). Approximately 15 – 40% of chronic hepatitis B patient will be cirrhotic and end stage liver disease (Maddrey, 2000; Gines *et al*., 2004). Cirrhotic and end stage liver disease caused by the development of liver fibrosis in chronic liver damage, concomitantly occur with excessive deposition of extracellular matrix (ECM) in the liver, and it will change the architecture of the liver and also develop regeneration nodules (Bataller & Brenner, 2005). Nowadays studies have shown reversible process of liver fibrosis (Hammel *et al*., 2001; Arthur, 2002; Pares *et al*., 1986; Dixon *et al*, 2004; Bataller & Brenner, 2005). Experimental studies in animal have shown that theraupetic target on hepatic stellate cell (HSC) can prevent the progressivity of liver fibrosis (Wu & Zern, 2000). Neutralization of HSC responded through inhibition of fibrotic signaling transduction is one of the way that probably provide benefits to liver fibrosis treatment and pentoxifylline is one of the drugs working by that way (Preaux *et al*., 1997; Mallat *et al*., 1995).

The expandable knowledge of the liver fibrosis process has resulted in noninvasive test of liver fibrosis by direct and indirect biomarker (Kelleher & Afdhal, 2000). Among indirect marker was APRI index that several study had shown the significant correlation (Spearman correlation γ=0.7) between APRI index and liver fibrosis degree in hepatitis B and C (Kelleher & Afdhal, 2000; Shin *et al*., 2008). To the best of our knowledge, there is no data on the influence of pentoxifylline to biomarker of liver fibrosis, especially APRI index. In that reason we perform study on the influence of pentoxifylline to APRI index in chronic hepatitis B.

MATERIALS AND METHODS

Patients

The patients were in-patient and out-patient chronic hepatitis B during February – August 2008 in Adam Malik Hospital Medan, with positive HBsAg at least 6 months after follow up (based on medical record). Clinical examination was performed concomitantly with routine blood, liver and renal

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function test and liver USG. The patients were included in the study provided their ages were more than 18 years and they agreed to join the study by informed consent. The patients were excluded from the study if they had history of cerebral and retinal bleeding, angina pectoris, less than 2 weeks post operation, had been using theophylline, cimetidine, warfarin and experienced decompensated cirrhotic.

Study design

This study was a clinical trial with pre dan post test design. The aim of the study was to examine the decrease of APRI index in chronic hepatitis B patients after 4 weeks treatment with 400 mg tid pentoxifylline and it would be used to decide the use of pentoxifylline as one of the antifibrotic agents in chronic liver disease.

$$APRI = \frac{AST\ level/ULN}{platelet\ count(10^9/L)}\ x\ 100.$$ The ULN in this study was 38 u/L.

Statistical analysis

To compare the decrease of APRI index before and after 4 weeks treatment of pentoxifylline, t test analysis was used for the data with normal distribution and Wilcoxon test for those with abnormal distribution.

RESULTS

1. Pre pentoxifylline treatment

From the baseline data we had found that the mean age of subject studied was 48.31 years (9 males and 2 females). The mean of values of AST, ALT and total bilirubin were above normal level, i.e AST 91.82 u/L, ALT 64.64 u/L and total bilirubin 1.68 mg/dL.

Table 1. Baseline characteristic of the study subject

Parameter		Mean (x±SD)	Range
S e x	(male :female)	9 : 2	
A g e	(years)	48.31±12.80	25 – 72
Haemoglobin	(N ♂ = 14 -18; ♀= 12 – 16 g/dL)	12.72±2.65	6.50 – 16.30
Platelet	(N 150 – 450.10⁹/L)	210.64±52.85	117 – 308
A S T	(N <30 u/L)	91.82±100.16	18 – 355
A L T	(N <50 u/L)	64.64±49.61	16 – 165
Total bilirubin	(N <1,30 mg/dL)	1.68±2.01	0.53 – 7.39
Albumin	(N 4,6 – 5,4 g/dL)	4.42±0.86	2.84 – 5.49
C r e a t i n i n e	(N 0,7 – 1,2 mg/dL)	1.27±0.77	0.58 – 2.86
		1.17±1.07	0.19 – 3.17
APRI Index			

N = normal value

The mean APRI index was 1.17 ranging from 0.19 to 3.17

2. Post pentoxifylline treatment

In this study the AST level increased after 4 weeks pentoxifylline treatment (91.82±100.16 *vs* 97.91±146.75; p=0.79), contratry to ALT and total bilirubin which decreased *i.e* 64.64±49.61 vs 50.64±26.13 (p=0.28) and 1.68±2.01 *vs* 0.74±0.30; (p=0.008) respectively.

Table 2. The data of mean,range pre and post 4 weeks pentoxifylline treatment and statistic p value

Parameter	Pre Pentoxifylline	Post Pentoxifylline	P
Platelet (a)			
a. Mean (10^3)	210.64±52.85	207.45±57.01	
b. Range (10^3)	117 – 308	114 – 294	0.84
AST (b)			
a. Mean	91,82±100.16	97.91±146.75	
b. Range	18 – 355	22 – 490	0.79
ALT (b)			
a. Mean	64.64±49.61	50.64±26.13	
b. Range	16 – 165	25 – 104	0.28
Total bilirubin (b)			
a. Mean	1.68±2.01	0.74±0.30	
b. Range	0.53 – 7.39	0.33 – 1.26	0,008*
Albumin (a)			
a. Mean	4.42±0.86	4.69±0.52	
b. Range	2.84 – 5.49	3.75 – 5.41	0.37
Creatinine(b)			
a. Mean	1.28±0.77	1.09±0.61	
b. Range	0.58 – 2.86	0.51 – 2.25	0.01*
APRI Index(b)			
a. Mean	1.17±1.07	1.31 ±1.84	
b. Range	0.19 – 3.17	0.23– 5.55	0.96

*Significant statistically

As shown in Table 2, APRI index increased after 4 weeks pentoxifylline treatment (1.17±1.07 *vs* 1.31±1.84; p=0.96). Surprisingly, an increased of albumin level (4.42±0.86 *vs* 4.69±0.52; p=0.37) was observed.

DISCUSSION

Pentoxifyllline, 1-(5-oxohexyl)-3,7-dimethylxanthine, is an analog of methylxanthine theobromine. Pentoxifylline is widely use in North America since 1982 to improve blood capillary circulation in claudicatio intermittent (Hinze *et al.*, 1972). Adams *et al* (2004) had shown that pentoxifylline in nonalcoholic steatohepatitis (NASH) at the dose 1600 mg/day for 12 months could decrease aminotransferase level. Satapathy *et al* (2004, 2007) had shown also in NASH that ALT and AST had decreased after 4 weeks treatment of pentoxifylline 400 mg tid and still constantly decrease until 12 months of treatment. Contrary to this study, pentoxifylline could decrease ALT level (64.64±49.61 vs 50.64±26.13;p=0.28) but not AST level (91,82 ±100.16 vs 97.91±146.75;p=0.79). The difference

of pentoxifylline effect on ALT compare to AST is not quitely clear.

Shin *et al* (2008) showed that APRI index was the most accurate indirect marker for predicting significant liver fibrosis in chronic hepatitis B. The cut-off value of APRI >1.4 has positive predictive value (PPV) 84% for predicting significant fibrosis and APRI <0.5 has negative predictive value (NPV) 91.3% for excluding significant fibrosis. In this study, we found that pentoxifylline as antifibrotic agent in the liver didn't decrease the APRI index score. This could happen because the component of APRI didn't match the effect of pentoxifylline on AST and platelet in other previous studies. The study of Austin AS *et al* (2004) showed that treatment of pentoxifylline with the dose 1800 mg once a day for 2 weeks in 12 compensated alcoholic cirrhotic patients could increase platelet from 76 (56 – 131) to 80 (66 – 243). The study of Satapathy *et al* (2004, 2007) showed in NASH that AST were decreasing along with ALT after 4 weeks treatment of pentoxifylline 400 mg tid and still constantly decrease until 12 months of treatment. Contrary to this study, pentoxifylline had slightly decreased the platelet of chronic hepatitis B patients (210.64±52.85 vs 207.45±57.01; p=0.84) while AST increased accordingly (91.82±100.16 *vs* 97.91±146.75; p=0.79). The difference observed in this study might be influenced by the difference of subjects involved in the other studies. The subjects in this study also showed varying APRI index range, from 0.19 to 3.17 revealing different stage of fibrosis. Whether pentoxifylline had reverse effect in nonsignificant liver fibrosis of chronic viral hepatitis, still be a question and need more study to prove. In this study, the use of pentoxifylline as antifibrotic agents in chronic viral hepatitis was not proven.

Summary

Treatment of pentoxifylline for 4 weeks as antifibrotic in chronic hepatitis B patients measured by APRI index was not proven. It might be due to increase of AST slight decrease of the platelet after treatment. More studies need to be carried out to prove the exact effect of pentoxifylline in liver fibrosis particularly in chronic viral hepatitis. In addition other direct and indirect biomarkers of liver fibrosis should be measured.

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