Chinese Medical Journal 1998; 111(3): 248-251

Effectiveness of the analogue of natural Schisandrin C (HpPro) in treatment of liver diseases: an experience in Indonesian patients

Nurul Akbar, Rino Alvani Gani Tahir, Widayat Djoko Santoso, Soemarno, Sumaryono, H.M. Sjaifoellah Noer and Liu Gengtao 刘耕陶

Objective To determine the effect of dimethyl-4, 4'-dimethoxy-5, 6, 5', 6-dimethylene dioxybiphenyl-2, 2'-dicarboxylate (HpPro) on patients with acute and chronic liver diseases.

Methods An open trial and a prospective randomized and controlled study were performed. The open trial consisted of 56 cases (16 cases of acute hepatitis, 20 cases of chronic hepatitis, 14 cases of liver cirrhosis and 6 cases of fatty liver). Controlled study consisted of 20 cases of Child A chronic hepatitis which were randomly treated with either HpPro or a mixture of known drugs which used as a liver protective agent in Indonesia as control for one week. The patients were then crossed over those two drugs in the next week.

Results In the open trial, after 4 weeks' treatment with HpPro 7.5 mg orally three times daily, acute hepatitis, chronic hepatitis and fatty liver cases showed rapid decrease of SGOT and SGPT. In the liver cirrhosis cases, SGOT and SGPT were decreased slowly. In the controlled trial, nine patients received HpPro 7.5 mg three times daily orally and eleven were treated with a mixture of known drugs as the controls. After one week treatment, HpPro group clinically showed significant decrease of SGPT and SGOT levels compared to control group ($P = 0.035$). At the second week, HpPro group showed significant decrease of SGOT compared to control group ($P = 0.038$) but the decrease of SGPT was not significant ($P = 0.096$).

Conclusion Treatment with HpPro is effective to reduce liver impairment in acute and chronic liver diseases on Indonesian patients. No side effect of HpPro was observed.

Chin Med J 1998; 111(3): 248-251

Dimethyl-4, 4'-dimethoxy-5, 6, 5', 6-dimethylene dioxybiphenyl-2, 2'-dicarboxylate (HpPro) is an analogue of schisandrin C which is one of the components isolated from the traditional Chinese tonic *Fructus Schisandrae*.[1] It was demonstrated that HpPro protects the liver of experimental animals against toxic agents e. g., CCl_4 and D-galactosamine.[2] Clinical study indicated that HpPro is effective in improving patient's symptoms and impaired liver functions such as elevated transferase enzymes and bilirubin, low albumin level, and increased alpha fetal-protein.[3-7] Several studies were done to compare the effectiveness of the analogue of Schisandrin C with glycirrhizin and silymarin.

In this paper we report an open trial of the HpPro and a prospective, controlled, randomized study to asses the efficacy of HpPro in the treatment of liver diseases among Indonesian patients.

METHODS

This study was divided into two steps. The first step was an open trial which included various liver diseases, and the second step was a randomized, prospective, controlled study, in which patients with Child A[8] chronic hepatitis were randomly assigned to receive HpPro or to be treated with a kind of mixture of drugs as controls.

Acute hepatitis was confirmed by elevation of SGOT (serum glutamic-oxaloacetic transaminase) and SGPT (serum glutamate pyruvate transaminase) more than 10 times the normal level, positive hepatitis markers such as IgM Anti-HAV or IgM anti-HBc and ultra-sonography (USG) find-

Department of Internal Medicine, School of Medicine, University of Indonesia, Jalan Salemba No. 6, Jakarta 10310, Indonesia (Akbar N, Tahir RAG, Santoso WD, Sumaryono and Noer SHM)

Department of Internal Medicine, Sint Carolus Hospital, Jakarta, Indonesia (Soemarno)

Department of Pharmacology, Institute of Materia Medica, Chinese Academy of Medical Sciences, Beijing 100050, China (Liu GT)

ings. The diagnosis of chronic hepatitis was confirmed by clinical findings (abnormality of transferase enzymes for more than 6 months), USG and some by CT scan. No liver biopsy was performed. The diagnosis of liver cirrhosis and fatty liver was confirmed by USG and in some cases by liver biopsy. At entry into the study, the severity of the liver disease was classified using the Child criteria.[8] We did not assess the effect of the drug on the viral load.

Pregnant and lactating women were not included. Patients with evidence of uncontrolled, clinically significant cardiovascular, pulmonary, renal, pancreatic, metabolic, neurological, endocrine or other systemic diseases were excluded. Patients were to be 17 years or older and were required to give oral or written informed consent. The normal levels for SGOT and SGPT were 22 IU/L and 18 IU/L, respectively.

HpPro capsules were obtained from the Institute of Materia Medica, Chinese Academy of Medical Sciences, Beijing, China.

Open trial

All cases with various liver diseases such as acute hepatitis, chronic hepatitis, liver cirrhosis and fatty liver were treated with HpPro three times 7.5 mg daily, orally for four weeks between August 1996 and December 1996. SGOT and SGPT were determined on the entry to the study and every week until the end of the study.

Controlled trial

The study group was treated with HpPro capsules three times 7.5 mg daily, orally, for the first week and the control group received a drug consisting of methionine 100 mg, choline bitartrate 100 mg, aneurine HCl 2 mg, Vit B_2 2 mg, nicotinamide 6 mg, Vit B_6 2 mg, panthenol 3 mg, biotin 0.1 mg, folic acid 0.4 mg, Vit B_{12} 0.67 μg and Vit E 3mg which is known and used as a liver protective agent in Indonesia.

We crossed over the two regiments in the next week without any washing period. On admission and at the end of the first and second week of the study, an examination was performed, with assessment of general condition, SGOT and SGPT. Student t test was applied to analyze sex and age as well as SGPT and SGOT levels variable.

Patients showing reduction of transferase enzymes more than 40 % were classified as improved, less than 40 % or an increase after treatment as failure. Chi-squares test (with Fisher exact, 1-tailed) was used to compare the clinical improvement between the two groups.

RESULTS

Open trial

Fifty-six cases with liver diseases were included in this open study. The background of the patients is shown in Table 1. All cases showed declines of SGOT and SGPT except for two cases of liver cirrhosis and one case of chronic hepatitis.

Table 1. Characteristic of subjects in the open trial

	Acute hepatitis	Chronic hepatitis	Liver cirrhosis	Fatty liver
No. of cases	16	20	14	6
Sex				
Male	7	9	7	3
Female	9	11	7	3
Age				
Minimal	17	26	36	28
Maximal	60	68	76	54
$\bar{x} \pm s$	31.0 ± 12.0	42.2 ± 13.9	61.3 ± 13.9	34.6 ± 16.5

Tables 2 and 3 showed the mean and standard deviation of SGOT and SGPT level during the study. As shown in Tables 2 and 3, transferase enzymes in acute hepatitis became normal after 2 weeks treatment with HpPro capsules. In patients with chronic hepatitis and fatty liver SGOT and SGPT became normal within 4 weeks except for 1 (5%) case of chronic hepatitis. Decline of SGOT and SGPT to normal level were shown in 4 (28.6%) cases of liver cirrhosis in the four weeks' study.

Table 2. The effect of HpPro on the level of SGOT of Indonesian patients in an open trial ($\bar{x} \pm s$)

Week	Acute hepatitis (n = 16)	Chronic hepatitis (n = 20)	Liver cirrhosis (n = 14)	Fatty liver (n = 6)
0	111.1 ± 163.6	48.0 ± 51.8	61.2 ± 33.1	32.9 ± 15.1
1	56.5 ± 82.5	42.4 ± 46.2	44.9 ± 23.3	27.7 ± 13.8
2	24.0 ± 9.0	31.1 ± 32.8	44.5 ± 26.9	21.6 ± 9.3
3	20.7 ± 5.2	35.2 ± 30.0	58.0 ± 22.6	18.7 ± 8.2
4	16.3 ± 2.2	20.0 ± 5.7	37.8 ± 18.3	13.7 ± 5.6

Table 3. The effect of HpPro on SGPT level of Indonesian patients in an open trial ($\bar{x} \pm s$)

Week	Acute hepatitis (n = 16)	Chronic hepatitis (n = 20)	Liver cirrhosis (n = 14)	Fatty liver (n = 6)
0	194.1 ± 212.6	69.2 ± 74.4	45.3 ± 18.0	43.3 ± 21.2
1	80.7 ± 122.5	63.1 ± 88.4	33.3 ± 17.5	33.0 ± 15.4
2	33.8 ± 16.9	40.1 ± 45.6	27.4 ± 10.0	25.0 ± 11.3
3	13.3 ± 4.5	27.2 ± 27.4	27.1 ± 9.2	21.1 ± 10.1
4	14.4 ± 3.7	20.6 ± 2.8	25.6 ± 4.7	16.3 ± 7.2

Controlled trial

Twenty patients were included during the two months of

Chinese Medical Journal 1998; 111(3):248-251

study and completed the two-week study period. Nine patients were treated with HpPro and 11 patients were treated with the mixture of drugs described above as control.

The two groups were well matched regarding to age and sex. (Tables 4 and 5). Clinical characteristics were shown in Table 5. We could not match the etiology and the liver under-lying disease because of the small number of the samples and time constraints.

Table 4. Characteristic of subjects on entry of the controlled trial*

	HpPro group	Control group
Sex		
Male	5	9
Female	4	2
Age		
Minimal	28	26
Maximal	70	67
$\bar{x} \pm s$	44.0 ± 15.4	46.8 ± 15.7

* Based on Student t test. No significant differences between HpPro and control groups.

Table 5. Clinical characteristics of subjects on entry of the controlled trial

	HpPro group		Control group	
	No.	Column (%)	No.	Column (%)
Chronic hepatitis				
No	1	11.1	2	22.2
Yes	8	88.9	7	77.8
Liver cirrhosis				
No	8	88.9	9	77.8
Yes	1	11.1	2	22.2
HBsAg				
(-)	7	77.8	7	63.6
(+)	2	22.2	4	36.4
HBeAg				
(-)	9	100.0	11	100.0
(+)	0		0	
Anti-HbeAb				
(-)	8	88.9	9	77.8
(+)	1	11.1	2	22.2
Anti-HCV				
(-)	8	88.9	8	72.2
(+)	1	11.1	3	27.8

The changes of SGOT and SGPT were shown in Tables 6 and 7. After one week of treatment, clinically HpPro group showed decreases of SGPT and SGOT levels by 88.9% and 77.8%, respectively, compared to 17.6 % and 11.8% in the control group. The differences of SGPT and SGOT between HpPro and control groups are highly significant (P = 0.009 and P = 0.035).

In the second week, the HpPro group showed 90.9% decrease of SGOT compared to 44.4% of the control group (P = 0.038), but the decrease of SGPT was not significant

Table 6. SGOT and SGPT levels on the controlled trial at the first week ($\bar{x} \pm s$)

	HpPro (n = 9)	Control (n = 11)
SGOT		
on entry	57.6 ± 40.0	51.5 ± 22.4
at the end of the 1st week	38.0 ± 22.8	61.6 ± 18.9
SGPT		
on entry	55.9 ± 65.9	61.6 ± 19.0
at the end of the 1st week	46.3 ± 46.6	79.5 ± 75.2

Table 7. Comparison of therapeutic effect between the HpPro group and the control group in the controlled study on chronic hepatitis

	No. of cases	Improved (%)	Not improved (%)	P*
The first week				
SGPT				
HpPro	9	8(88.9)	1(11.1)	0.009
Control	11	3(27.3)	8(72.7)	
SGOT				
HpPro	9	7(77.8)	2(22.2)	0.035
Control	11	3(27.3)	8(72.7)	
The second week				
SGPT				
HpPro	11	10(90.9)	1(9.1)	0.096
Control	9	5(55.6)	4(44.4)	
SGOT				
HpPro	11	10(90.9)	1(9.1)	0.038
Control	9	4(44.4)	5(55.6)	

* Fisher exact: 1-tailed P value as compared with the corresponding control group.

(P = 0.098). In the first week, increased SGOT were found in 6 (54.5%) out of 11 cases of the control group compared to 2 (22.2%) out of 9 cases in HpPro group while increased SGPT were found in 6 (54.5%) out of 11 cases of the control group compared to 1 (11.1%) out of 9 cases in HpPro group. In the next week, increase of SGOT were found in 3 (33.3%) out of 9 cases in the control group compared to 1 (9.1%) out of 11 cases in HpPro group, while increased SGPT were found in 4 (44.4%) out of 9 in the control group compared to 1 (9.1%) out of 11 in the HpPro group. Both drugs were well tolerated. No side effect was found.

DISCUSSION

The analogue of Schisandrin C (HpPro) was shown to protect experimental animals against various hepatoxins. The mechanism by which HpPro exerts its hepatoprotective action is still not well known, but it may be due to its inhibition of lipid peroxidation and covalent binding of CCl_4 metabolites to lipids of microsomes.[2]

The open trial of this observation showed rapid decrease of SGOT and SGPT in cases of acute hepatitis, chronic hepatitis and fatty liver. In liver cirrhosis cases, SGOT and SGPT decreased more slowly and did not drop to normal levels during this study. We assume that treatment for chronic hepatitis and especially liver cirrhosis needs higher doses of Hp-

Pro and a longer time of treatment which may have to be continued for 24 weeks.

The present controlled study demonstrated clinically that short-term treatment with HpPro decreased significantly SGOT and SGPT levels in chronic hepatitis compared to the control within one week. A controlled study that compared HpPro with Stronger Neo Minophagen C (SNMC) showed the same findings.[9] This study reported that twenty-four cases which were treated orally with HpPro for 8 weeks showed significant difference compared to 25 cases which were treated with SNMC. Another paired-controlled comparison of therapeutic effect between HpPro and Silymarin on chronic persistent hepatitis also showed significant difference.

The therapeutic effects of HpPro on chronic viral hepatitis B is also observed by double blind method.[10] Two groups of 20 patients were treated for two months in which the HpPro group showed remarkable improvement of liver function compared to the placebo group.

The present controlled study demonstrated clinically that short-term treatment with HpPro decreased significantly SGOT and SGPT levels in chronic hepatitis compared to the control within one week. Our controlled study showed statistically significant decrease of SGOT in the HpPro group in the first and the second week. However, SGPT levels was not decreased significantly in the second week. Although some studies performed in China showed a significant decrease of SGPT levels, our study only confirmed this result at the first week. This evidence may be due to short duration treatment or the small samples in our study. Nevertheless, our findings showed that increased SGOT and SGPT were more prevalent among the control group compared to HpPro group during the study period.

In conclusion, treatment with the analogue of Schisandrin C (HpPro) is effective in reducing liver impairment in acute and chronic liver diseases. Another controlled study with large samples and long duration may be necessary to establish the beneficial effects of HpPro on chronic liver disease therapy.

REFERENCES

1. Bao TT, Liu GT, Xu GF, et al. Studies on Fructus schizandrae: its effect on the increase of serum transaminase (SGPT) induced by chemicals. Natl Med J China 1974; 54:275.

2. Liu GT. From the study of Fructus schizandrae to the discovery of dimethyl-4, 4'- dimethoxy-5, 6, 5', 6' dimethylene dioxybiphenyl-2, 2'-dicarboxylate. Acta Pharm Sin 1983; 8:714.

3. Wang CF, Yang KZ, Wang LS. Clinical observations of dimethyl-4, 4'-dimethoxy-5, 6, 5', 6'-dimethylene dioxybiphenyl-2, 2'-dicarboxylate on viral hepatitis. Beijing Med J 1981; 3:206.

4. Zhang YX, Yu HQ , Shi JZ. Observations on the effects of dimethyl-4, 4'-dimethoxy-5, 6, 5', 6'-dimethylene dioxybiphenyl-2, 2'-dicarboxylate and honey pilula of silybum Marianum(L.) Gaertn on chronic viral hepatitis. Chin Modern Dev Trad Med J 1981: 1:24.

5. Wang CF, Zhang YX, Yu HQ, et al. Clinical observation of dimethyl-4, 4'-dimethoxy-5, 6, 5', 6'-dimethylene dioxybiphenyl-2, 2'-dicarboxylate. Tianjin Med J 1982; 2:93.

6. Zhang YX, Yao HQ , Xue HY. Treatment of chronic viral hepatitis and liver cirrhosis associated with high level of alpha fetal protein by using traditional medicines and dimethyl-4, 4'-dimethoxy-5, 6, 5', 6'-dimethylene dioxybiphenyl-2, 2'-dicarboxylate. Beijing Med J 1982; 4:255.

7. Wang CF, Chang YL. Clinical observations of the therapeutic effect of dimethyl-4, 4'-dimethoxy-5, 6, 5', 6'-dimethylene dioxybiphenyl-2, 2'-dicarboxylate on 56 cases of chronic viral hepatitis. New Drug Clin Remedies 1984; 3:205.

8. Child CG. The liver and portal hypertension. Philadelphia: Saunders, 1964: 50-53.

9. Wang KX, Nei CR, Hu AL, et al. Therapeutic effect of dimethyl-4, 4'-dimethoxy-5, 6, 5', 6'-dimethylene dioxybiphenyl-2, 2'-dicarboxylate on chronic viral hepatitis. New Drug Clin Remedies. 1986; 5:88.

(*Received July 8, 1997*)
本文编辑：张迎捷