

# Efficacy of intramuscular matrine in the treatment of chronic hepatitis B

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**BACKGROUND:** Hepatitis B virus (HBV) infection, a global public health problem, is the leading cause of cirrhosis and hepatocellular carcinoma (HCC) worldwide. There are more than 350 million HBV carriers in the world and up to one million die annually due to hepatitis B associated liver disease. So far no optimal treatment is available for patients with chronic hepatitis B. In the paper we investigated the efficacy of intramuscular matrine in the treatment of chronic hepatitis B.

**METHODS:** One hundred and twenty patients with chronic hepatitis B were randomly divided into matrine treatment group ( $n=60$ ) and control group ( $n=60$ ). The patients of the matrine group were given intramuscularly with matrine (an alkaloid extracted from a traditional Chinese herb *Radix Sophorae Flavescentis* by Guangzhou Ming Xing Pharmaceutical Factory, Guangzhou, China) of 100 mg daily for 90 days in addition to conventional liver-protective drugs including glucurone, inosine, compound vitamin B and caryophyllin. The control group received conventional liver-protective drugs alone. Clinical manifestations and laboratory parameters including liver biochemistry and serum hepatitis B virus markers were monitored before and after treatment in the two groups.

**RESULTS:** Significant differences were seen between the two groups in terms of improvement of clinical symptoms and signs, recovery of liver functions, and serum conversion from hepatitis Be antigen to HBe antibody and from positive to negative serum HBV DNA ( $P<0.05-0.01$ ). The result of the matrine group was more marked than that of the control group. Serious side-effects were not observed except mild pain at the site of injection of matrine in a few patients.

**CONCLUSION:** These results indicate that intramuscular matrine may be an economical, efficacious, safe drug for the treatment of chronic hepatitis B.

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**KEY WORDS:** chronic hepatitis B/therapy; matrine/therapeutical effect; HBV DNA; hepatitis B surface antigen; hepatitis Be antigen; seroconversion

## Introduction

It has been reported that matrine, an alkaloid extracted from a traditional Chinese herb *Radix Sophorae Flavescentis*, could protect experimental mice from the development of fatal hepatitis induced by lipopolysaccharides (LPS), inhibit the LPS-induced tumor necrosis factor (TNF) and interleukin-6 (IL-6) release,<sup>[1-3]</sup> and abate hepatic fibrosis.<sup>[4-7]</sup> The results of animal experiment and clinical studies have shown that oral or intravenous matrine can inhibit replication of hepatitis B virus (HBV) and improve biochemical abnormalities and fibrosis of the liver.<sup>[4-16]</sup> However, so far intramuscular matrine for the treatment of hepatitis B has rarely been reported. In this paper, we report the efficacy of intramuscular matrine in the treatment of patients with chronic hepatitis B.

## Methods

### Patients

Chronic hepatitis B was defined according to the criteria for prevention and treatment of viral hepatitis established at the Fifth National Conference on Infectious Diseases and Parasitic Diseases held in Beijing in 1995. Liver biopsy samples before and after treatment were collected from some patients. One hundred and twenty inpatients and outpatients with chronic hepatitis B from 3 hospitals (Affiliated Hospital of Guangdong Medical College, Zhanjiang, China; Haibin Centre Hospital, Zhanjiang, China; and Centre of Hepatology of Nanfang Hospital of First Military Medical University, Guangzhou, China) treated from January 1998 to December 1999 were randomly divided into matrine treatment group ( $n=60$ ) and control group ( $n=60$ ). All patients before treatment showed abnormal liver function and serum positive hepatitis B virus markers (HBVM) including hepatitis B

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surface antigen (HBsAg), hepatitis Be antigen (HBeAg), and/or hepatitis B virus DNA (HBV DNA). The two groups before treatment were comparable ( $P > 0.05$ ) in terms of sex, average age, duration of hepatitis, and grade of liver injury.

**Therapeutic methods**

Conventional liver-protective drugs including glucurone, inosine, compound vitamin B and caryophyllin were given orally in the two groups. The patients of the treatment group received intramuscular matrine injection (an alkaloid extracted from a traditional Chinese herb *Radix Sophorae Flavescentis* by Guangzhou Ming Xing Pharmaceutical Factory, Guangzhou, China) of 100 mg (4 ml) daily plus conventional liver-protective drugs for 90 days. The control group received conventional liver-protective drugs alone.

**Clinical manifestations and laboratory parameters**

Clinical manifestations included fatigue, anorexia, abdominal distention, hepatomegaly, and splenomegaly. Hematologic parameters included blood routine, serum alanine aminotransferase (ALT), serum total bilirubin (TBIL), albumin, A/G ratio, prothrombin activity (PA), blood urea nitrogen (BUN), and blood creatinine. Serum HBVMs (HBsAg, anti-HBs, HBeAg, anti-HBe, anti-HBc) were detected by enzyme-linked immunosorbent assay (ELISA), and HBV DNA was detected by polymerase chain reaction (PCR). Ultrasonic imaging of the liver, cholecyst, spleen and portal vein were also performed.

**Standards for effect evaluation**

Three grades of therapeutic effects were arbitrarily defined as marked effect, moderate effect and no effect. Marked effect: disappearance of symptoms of hepatitis, retraction or stabilization of hepatomegaly and spleno-

megaly, normalization and stabilization of serum ALT and TBIL levels three months after withdrawal of matrine; moderate effect: disappearance or remission of symptoms of hepatitis, stabilization of the sizes of the liver and spleen, decrease of serum ALT and TBIL levels by >50% of the initial values during treatment, but exacerbation after the withdrawal of the drug; no effect: non of the above-mentioned effects.

**Statistical analysis**

Wilcoxon's rank-sum test, the chi-square test and Student's *t* test were used for evaluating therapeutic effectiveness in the two groups. Exact probability was used when sample was less than 40 ( $n < 40$ ).

**Results**

**Clinical manifestations**

Clinical manifestations in the matrine group was improved more significantly than in the control group ( $P < 0.05-0.01$ , Table 1).

**Liver function**

Liver function in the matrine group was improved more significantly than in the control group ( $P < 0.05$ , Table 2).

**Serum HBVMs**

After treatment, negative conversion rates of HBeAg and HBV DNA and anti-HBe seroconversion rate in the matrine group were significantly higher than those in the control group ( $P < 0.01$ , Table 3).

**Total therapeutic efficacy**

The total effects (marked effect plus moderate effect) were higher significantly in the matrine group com-

**Table 1.** Improvement of symptoms and signs between the two groups (%)

Group	Fatigue	Anorexia	Abdominal distention	Hepatomegaly	Splenomegaly
Matrine	46/54(85.2)	49/56(87.5)	25/28(89.2)	26/34(76.5)	13/18(72.2)
Control	30/55(54.6)	32/54(59.3)	16/27(59.2)	15/33(45.5)	5/15(33.3)
$\chi^2$	12.118	11.294	6.531	6.784	
<i>P</i> value	<0.01	<0.01	<0.05	<0.01	0.0383 *

\* : Exact probability.

**Table 2.** Improvement of liver function between the two groups (%)

Group	ALT	TBIL	Albumin	PA
Matrine	51/60(85.0)	31/36(86.1)	19/23(82.6)	34/37(91.9)
Control	39/60(65.0)	23/35(65.7)	13/24(54.2)	28/38(73.7)
$\chi^2$	6.400	4.054	4.372	4.337
<i>P</i> <	0.05	0.05	0.05	0.05

**Table 3.** Conversion rate of serum HBVMs between the two groups (%)

Group	HBeAg negative conversion	Anti-HBe seroconversion	HBV DNA negative conversion
Matrine	33/58(56.9)	27/58(46.6)	17/38(44.7)
Control	7/59(11.9)	6/59(10.2)	5/40(12.5)
$\chi^2$	26.361	19.118	10.001
<i>P</i> <	0.01	0.01	0.01

**Table 4.** Total therapeutic efficacy between the two groups (%)

Groups	n	Marked effect	Moderate effect	No effect
Matrine	60	32(53.3)	20(33.3)	8(13.3)
Control	60	18(30.0)	21(35.0)	21(35.0)

$H_c=9.399$ ,  $P<0.001$ .

pared with the control group (86.7% vs 65.0%,  $\chi^2=7.685$ ,  $P<0.01$ ). Significant difference of total therapeutic efficacy between the two groups was also found by Wilcoxon's rank-sum test ( $H_c=9.399$ ,  $P<0.001$ , Table 4).

### Side-effects

No obvious side-effects were observed except mild pain at the site of matrine injection in a few patients. No leucopenia and thrombopenia occurred during the treatment in the two groups. In contrast, leukocytes count increased in 2 patients with leucopenia after matrine injection who had had no response to long-term oral administration of leucogen, vitamin B4, batilol (leukocytes count from  $2.3 \times 10^9/L$  before treatment to  $4.5 \times 10^9/L$  after treatment and from  $3.5 \times 10^9/L$  to  $4.6 \times 10^9/L$ , respectively). Renal function test showed normal levels of BUN and blood creatinine during the matrine treatment.

### Discussion

Chronic HBV infection affecting more than 350 million people worldwide and approximately 120 million people in China is the primary cause of cirrhosis and hepatocellular carcinoma (HCC) as well as one of the 10 leading causes of death.<sup>[17]</sup> Necroinflammation of the liver and progressive fibrosis are caused by persistent or intermittent HBV intrahepatic replication. Current therapies mostly focus on suppression of viral replication, which usually results in improvement of liver disease. So far no optimal treatment is available for patients with chronic hepatitis B. Interferon alfa and lamivudine (a nucleotide analogue) are acceptable antiviral drugs for inhibition of HBV replication. Interferon alfa has antiviral and immunomodulatory effects and lamivudine is a well-tolerated, orally administered agent that suppresses HBV replication. Both of drugs can induce virologic and biochemical remission in the treatment of chronic hepatitis B,<sup>[18-22]</sup> but in a way restricting their clinical utility because of being prone to relapse after the termination of treatment,<sup>[23]</sup> viral mutation,<sup>[24]</sup> costly price and/or frequent adverse effects.<sup>[25-28]</sup> As a result, it is important to probe into non-side-effect, economical, efficacious drugs for the treatment of chronic hepatitis B.

Matrine, an alkaloid extracted from a traditional

Chinese herb *Radix Sophorae Flavescens*, has been reported in the treatment of viral hepatitis. It could protect the D-galactosamine-treated mice and PA primed mice from the development of fatal hepatitis induced by LPS, and inhibit the LPS-induced TNF release from mouse peritoneal macrophages.<sup>[1,2]</sup> The results of clinical application of matrine in the treatment of chronic hepatitis B indicated that matrine given orally or intravenously can inhibit HBV replication with a negative conversion rate of serum HBV DNA and HBeAg as high as 55%<sup>[14]</sup> and improvement of liver biochemical levels.<sup>[4-16]</sup> However, intramuscular matrine for the treatment of hepatitis B has been rarely reported. The present study showed that clinical symptoms and signs in the matrine group was more significantly improved than in the control group; liver function test showed the improvement of levels of ALT, TBIL, albumin, A/G ratio and PA, negative conversion rate of HBeAg, HBV DNA and anti-HBe seroconversion rate were significantly higher in the matrine group than those in the control group ( $P<0.05-0.01$ ). No obvious side-effects were observed except mild pain at the site of matrine injection in a few patients. These results suggest that intramuscular matrine is a safe, economical, efficacious drug for the treatment of chronic hepatitis B.

Leukocytes count increased in two patients with leucopenia after matrine injection who had had no response to long-term oral administration of leukogenic drugs, suggesting that matrine could promote leukocytopoiesis in patients with chronic HBV infection complicated by leucopenia, a striking feature differing from interferon alfa per se bringing leucopenia during the course of treatment. It may be presumed that matrine is better indicated for patients with chronic hepatitis B associated with leucopenia but interferon alfa is a relative contraindication for these patients with leucopenia.

Pharmacologically, the mechanism of matrine in treating viral hepatitis is not very clear. The possible effects of matrine may include direct inhibition of viral replication<sup>[8,10,15]</sup> because its chemical structure resembles purine which interferes viral nucleic acid synthesis; immunomodulatory effects;<sup>[16,29]</sup> inhibition of LPS-induced TNF release, accordingly remission of necroinflammation of the liver;<sup>[1,2]</sup> blocking of hepatocytes apoptosis;<sup>[30]</sup> and suppression of intrahepatic collagen synthesis, consequently anti-fibrogenesis.<sup>[4-7]</sup> In one patient of this study ultrasonography of the liver before treatment revealed chronic active hepatitis associated with early cirrhosis. After 3-month injection of matrine, ultrasonography of the liver showed obvious improvement of liver fibrosis and concomitant virological response, suggesting the effects of matrine on fibrogenesis, necroinflammation, and HBV replication. However, the efficacy of intramuscular matrine in the treatment of chronic hepatitis B awaits further study.

## Competing interest

The author or authors do not choose to respond to the statements listed in Instructions for Authors.

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