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Ademetionine 1,4-Butanedisulphonate *vs* Traditional Chinese Medicine for the Treatment of Acute Viral Hepatitis with Hepatocellular Jaundice

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Abstract

Objective: To compare the efficacy of ademetionine 1,4-butanedisulphonate (Ade-SD_4) versus a traditional Chinese remedy (TCR) in patients with hepatocellular jaundice associated with acute viral hepatitis.

Patients: 253 patients were enrolled and 148 completed the study.

Methods: In this randomised, open-label, multicentre, parallel-group study, patients (aged 14 to 65 years) with elevated serum bilirubin levels (>2 × upper limit of normal) received either Ade-SD_4 (ademetionine 1g) intravenously once daily for 2 weeks then oral Ade-SD_4 (ademetionine 0.5g) twice daily for 4 weeks, or TCR (Capillarin, a herbal derivative, 30ml intravenously once daily for 2 weeks, then oral Capillarin 30ml for 4 weeks plus six tablets of Tanshinone, a *Salvia miltiorrhiza* derivative, once daily throughout the 6 weeks). Treatment efficacy was evaluated by changes in serum bilirubin (total and conjugated) and transaminases, fatigue and jaundice after 7, 14, 28 and 42 days.

Results: Both Ade-SD_4 (n = 132) and TCR (n = 121) significantly improved serum transaminases, albumin, alkaline phosphatase, γ-glutamyl transferase and total bile acids; improvements in serum total and conjugated bilirubin and alanine amino transferase (ALT) were significantly greater with Ade-SD_4 than with TCR. After 7 days of treatment, median total bilirubin was 2.23 mg/dl in Ade-SD_4-treated patients *vs* 3.08 mg/dl in TCR-treated patients ($p = 0.0001$), while conjugated bilirubin and ALT were, respectively, 0.97 *vs* 1.5 mg/dl ($p = 0.0001$) and 116 *vs* 162 U/L ($p = 0.0006$). At day 7, the proportion of serum total and conjugated bilirubin responders was significantly higher in the Ade-SD_4 group (69 and 73%, respectively) than in the TCR group (50 and 54%, respectively; $p \leq 0.004$). Significant differences in favour of Ade-SD_4 were observed for jaundice ($p = 0.01$), fatigue ($p = 0.004$), general discomfort ($p = 0.05$), urinary discoloration ($p = 0.02$), nausea ($p = 0.01$), anorexia ($p = 0.001$), and patient ($p = 0.01$) and physician ($p = 0.05$) assessments of treatment efficacy. Both treatments were well tolerated and no serious adverse effects were reported.

Conclusion: Ade-SD_4 is significantly more effective than TCR in reducing the severity and duration of hepatocellular jaundice associated with acute viral hepatitis.

Acute viral hepatitis is a systemic infection of the liver that is caused by specific viruses with relative or absolute predilection for the hepatocyte.[1] Patients with acute viral hepatitis exhibit hepatocellular dysfunction and hepatocellular jaundice, and complain of profound anorexia, fatigue, nausea, vomiting and fever. Urinary discoloration typically occurs some 3 to 10 days prior to the onset of hepatocellular jaundice. The latter condition is characterised by increased bilirubin levels, pruritus and jaundice, which can last for several weeks.[1] The clinical presentation of acute viral hepatitis varies only slightly, regardless of the causal virus.

Although most patients with acute viral hepatitis are treated at home, many require hospitalisation for severe malaise, fatigue, anorexia, vomiting, dehydration, jaundice and abdominal pain during the acute phase of the disease. Traditional remedies are commonly used in China for the treatment of liver disease, with the purpose of alleviating symptoms and improving biochemical markers of hepatocellular jaundice.[2-4]

Ademetionine, also known as S-adenosyl-L-methionine or SAMe, a physiological compound synthesised in the liver from methionine and adenosine triphosphate by the enzyme SAMe synthetase,[5] plays a central role in the control of transmethylation and trans-sulphuration,[6] and thus in the regulation of membrane fluidity and the activity of Na+/K+ ATPase.[7,8] In addition, ademetionine promotes the cellular bioavailability of sulphates, thereby promoting trans-sulphuration reactions and detoxification processes in the hepatocyte.[9]

Liver disease primarily reduces the activity of SAMe synthetase and phospholipid methyltransferase,[10] resulting in decreased levels of ademetionine, reduced hepatic detoxification, and reduced biliary secretion. Studies conducted in cholestatic patients have shown that exogenously administered ademetionine can effectively reduce serum levels of total bile salts, bilirubin and transaminases, and ameliorate pruritus.[11-14]

Ademetionine shows anticholestatic activity.[6,15] In detail, placebo-controlled studies have demonstrated that ademetionine significantly improves serum levels of transaminases and total and conjugated bilirubin, indicating that it is an effective agent for the treatment of liver disease with accompanying jaundice.[12,13,16-19]

The present study was designed to determine whether ademetionine 1,4-butanedisulphonate (Ade-SD_4), a stable ademetionine salt, administered intravenously and orally, was more effective than a traditional Chinese remedy (TCR; Capillarin, a herbal derivative, plus Tanshinone, a *Salvia miltiorrhiza* derivative) in improving the biochemical parameters, as well as the subjective and objective symptoms, of acute viral hepatitis with associated hepatocellular jaundice. In addition, the study evaluated the tolerability of Ade-SD_4 and TCR.

Patients and Methods

Study Design

The study was designed as a multicentre (25 Chinese centres), randomised, open-label comparative trial conducted over 6 weeks in patients with acute viral hepatitis and hepatocellular jaundice. The study was performed in accordance with the principles of the Declaration of Helsinki (1964), Guidelines for Good Clinical Practice for Study on Medicinal Products in the European Community (1990), and Chinese laws and regulations.

Study Participants

Male and female patients aged 14 to 65 years with a diagnosis of acute viral hepatitis A and E confirmed by immunological markers and complicated by hepatocellular jaundice, defined as a sustained (>1 week) serum total bilirubin (STB) of twice the upper limit of normal, were eligible to enter the study. Patients provided verbal or written consent in the presence of a witness.

Patients were excluded from the study if they fulfilled one or more of the following criteria: acute hepatitis other than hepatitis A or E; fulminant hepatitis or decompensated liver disease; STB

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levels greater than 10 times the upper limit of normal; alcohol (≥60 g/day) or drug abuse; extrahepatic cholestasis; severe concomitant or neoplastic disease; concomitant skin conditions causing pruritus; and concomitant corticosteroid treatment.

Patients were permitted to continue taking concurrent medication that did not conflict with the exclusion criteria as long as the dose and the dosage regimen were constant throughout the study.

Treatment

Eligible patients were randomised to receive either Ade-SD_4 or TCR (Capillarin plus Tanshinone). A single randomisation list was produced for all planned patients, assigning numbers to either Ade-SD_4 or TCR according to a block randomisation procedure. Each centre was provided with a section of this list and assigned each patient to a consecutive randomisation number according to the order in which they were enrolled.

Patients in the Ade-SD_4 group received an intravenous infusion of Ade-SD_4 (ademetionine 1g in 250ml of 5% glucose or saline solution) once daily for the first 2 weeks and then for the remaining 4 weeks received one enteric-coated Ade-SD_4 tablet (containing 0.5g of ademetionine) twice daily with water at meal times. The Ade-SD_4 solution for intravenous administration was freshly prepared each day from reconstituted lyophilisate and stored for no more than 2 hours after preparation.

The TCR treatment regimen involved administration of Capillarin 30ml once daily in the morning (intravenously for the first 2 weeks, then orally for the remaining 4 weeks) plus six tablets of Tanshinone once daily for 6 weeks.

Efficacy Measurements

The following biochemical parameters and symptoms were used to evaluate treatment efficacy in patients with acute hepatitis with hepatocellular jaundice.

The primary efficacy variables were symptoms of pruritus, fatigue and jaundice, and the following biochemical parameters: serum levels of total and conjugated bilirubin (STB and SCB, respectively), glutamic oxalacetic and pyruvic transaminases [aspartate amino transferase (AST) and alanine amino transferase (ALT), respectively], and the time to normalisation of transaminases or their reduction to <50% of the upper limit of normal.

Secondary efficacy variables comprised other symptoms of liver disease (liver tenderness, urinary discoloration, paleness of stools, nausea, vomiting, anorexia, diarrhoea, hepatomegaly, splenomegaly and general discomfort), serum levels of alkaline phosphatase (ALP), γ-glutamyl transferase (γ-GT) and albumin (ALB), and plasma prothrombin time (PT).

Serum levels of STB, SCB, AST and ALT were measured at the pre-study visit and every 7 days throughout the 42-day study. Plasma PT and serum ALP, γ-GT and ALB were measured at the pre-study visit and after 14 and 42 days of treatment.

Symptoms of liver tenderness, urinary discoloration, paleness of stools, jaundice, nausea, vomiting, anorexia, diarrhoea, fatigue and pruritus were assessed every 7 days using an ordinal scale. Hepatomegaly and splenomegaly were graded in terms of the distance from the liver edge and splenic tip, respectively, to the costal margin. Fever and pruritus were reported as absent or present. General discomfort was evaluated using a visual analogue scale.

Treatment response (expressed as time to normalisation or reduction of serum amino transferases to within twice the upper limit of normal or the time to normalisation or reduction of serum bilirubin to <50% of the baseline level) and time to recovery were monitored throughout the study.

Tolerability

The following tolerability parameters were evaluated at the pre-study visit and after 14 and 42 days of treatment: serum total protein, glucose, urea, total bile acids, ammonia and haemoglobin, and whole blood cell and platelet counts. Urinary

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levels of protein, glucose, ketones, bilirubin and haemoglobin were determined at the same timepoints.

Statistical Analysis

The study was planned to recruit a total of 250 patients on the basis of an expected reduction in serum total bilirubin of 77% in the Ade-SD_4 group and 55% in the TCR group after 2 weeks of treatment, a dropout rate of 25%, a statistical power of 90% and a significance level of 5% (two-tailed test).

Intergroup comparisons of baseline values were performed using an analysis of variance and the Mann-Whitney non-parametric test for quantitative variables, and the chi-square test for qualitative variables.

Efficacy was assessed for the intention-to-treat population (defined as those patients who had undergone at least one efficacy assessment after initiation of treatment). If successive values were missing, the last available data value was substituted in accordance with the Last Observation Carried Forward (LOCF) method. Efficacy between treatments was recorded either as a significant amelioration of both the biochemical parameters (STB, SCB, AST and ALT) and objective and subjective symptoms (jaundice, pruritus and fatigue), or as a significant reduction in response time.

Confirmatory analysis focused on changes in STB, SCB, AST and ALT over the first week of intravenous treatment. For each primary variable, an analysis of co-variance was performed using treatment and centre as the factors and the baseline value as the co-variant. Confidence intervals were set at 95% and p-values were interpreted in a descriptive manner. The treatment effect at other times was analysed in a similar manner. Time to recovery was assessed by survival analysis and the

Table I. Patient demographics and baseline characteristics (intent-to-treat population). Data are presented as mean ± standard deviation, unless otherwise stated

Patient characteristics	Ade-SD_4 (n = 132)	TCR (n = 121)
Age (y)	36.5 ± 12.1	35.9 ± 12.8
Male (%)	71	64
Blood pressure (mm Hg)		
Systolic	116.7 ± 13.5	167.6 ± 14.4
Diastolic	74.7 ± 7.8	75.4 ± 8.3
Heart rate (beats/min)	78.2 ± 5.5	78.1 ± 5.5
Body temperature (°C)	36.8 ± 0.4	36.7 ± 0.4
Acute viral hepatitis (n)		
A	83	82
E	34	31
A + E	4	0
Other/not defined	11	8
STB (mg/dl)	6.5 ± 3.6 (5.7†)	6.7 ± 3.7 (5.8†)
SCB (mg/dl)	3.6 ± 2.1 (3.0†)	3.9 ± 2.7 (3.0†)
AST (U/L)	517.6 ± 556.2 (314.8†)	721.9 ± 876.4* (422.7†)
ALT (U/L)	865.4 ± 697.9 (603.7†)	1056 ± 1021.9 (681.2†)
Fatigue (%)	114 (86)	107 (88)
Jaundice (%)	125 (95)	115 (94)
Pruritus (%)	20 (15)	12 (10)

Ade-SD_4 = ademetionine 1,4-butanedisulphonate; **ALT** = alanine amino transferase; **AST** = aspartate amino transferase; **SCB** = serum conjugated bilirubin; **STB** = serum total bilirubin; **TCR** = traditional Chinese remedy.
* significant difference between treatment groups ($p < 0.05$); † = geometric mean.

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survival functions were compared using the log-rank test. Secondary efficacy variables were evaluated according to the type of data and its distribution.

The analysis of tolerability was performed on all randomised patients who had received at least one dose of study medication, using descriptive statistics of all reported adverse events and laboratory findings.

Results

Patients

Patient demographics are summarised in table I. There were statistically significant differences in the level of AST and incidence of pruritus between the treatment groups at baseline.

A total of 253 patents were randomised to treatment (132 to Ade-SD_4 and 121 to TCR) and 148 patients completed the study. All randomised patients (n = 253) were included in the intention-to-treat (ITT) efficacy analysis and in the tolerability analysis.

Biochemical Endpoints

Ade-SD_4 was significantly more effective than TCR at reducing serum bilirubin levels in patients with acute viral hepatitis with associated hepatocellular jaundice. A statistically significant difference in favour of Ade-SD_4 was observed for both STB (fig. 1a) and SCB (fig. 1b) at 7, 14, 28 and 42 days.

After treatment for 7 days, 69% of patients in the Ade-SD_4 group were STB responders (fig. 2a) and 73% were SCB responders (fig. 2b) compared with 50 and 54%, respectively, in the TCR group ($p = 0.004$ and $p = 0.003$, respectively). The survival analysis of the time to response for STB showed that Ade-SD_4 was significantly superior to TCR ($p = 0.001$).

Following treatment for 7 days, serum transaminases decreased significantly from baseline values in both treatment groups and subsequently continued to fall. A significant treatment effect in favour of Ade-SD_4 over TCR was noted with regard to ALT levels at each assessment point of the study, whereas no significant intergroup differences in AST levels were recorded during treatment (fig. 3).

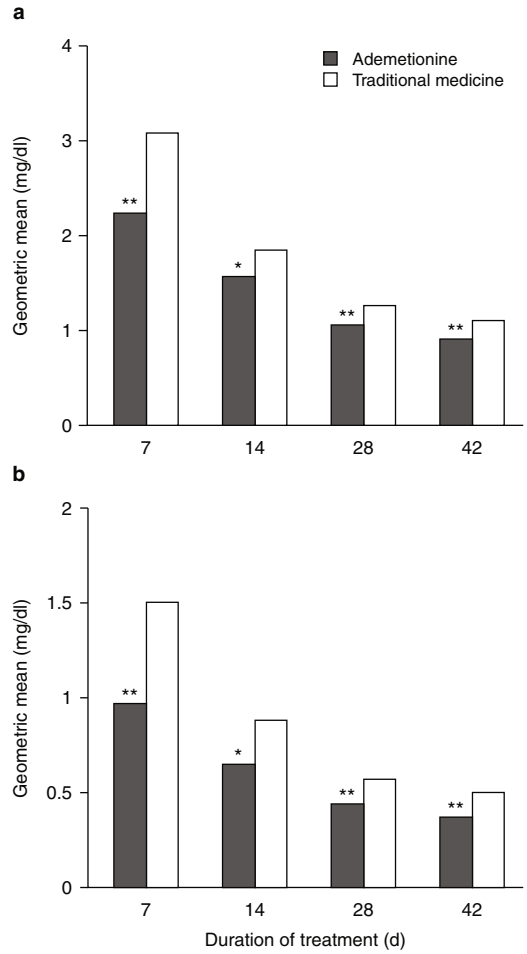

Fig. 1. Effects of ademetionine 1,4-butanedisulphonate or traditional Chinese medicine on serum total (**a**) and conjugated (**b**) bilirubin levels in patients with acute viral hepatitis associated with hepatocellular jaundice. The difference between treatments was set at * $p < 0.05$ and ** $p < 0.01$.

Compared with baseline values, Ade-SD_4 and TCR significantly improved serum levels of ALB, ALP, γ-GT and total serum bile acids (TSBA) and plasma PT ($p \leq 0.01$ for each variable), but there

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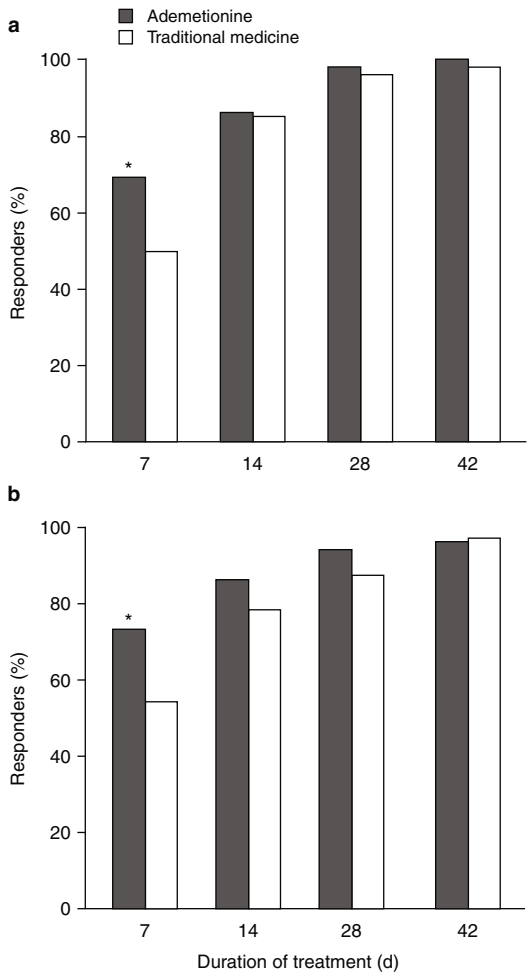

Fig. 2. Percentages of serum total (**a**) and conjugated (**b**) bilirubin 'responders' following treatment with ademetionine 1,4-butanedisulphonate or traditional Chinese medicine in patients with acute viral hepatitis associated with hepatocellular jaundice. The difference between treatments was set at * p = 0.004 for (**a**) and * p = 0.003 for (**b**). Responders were defined as patients whose serum bilirubin levels normalised or were reduced to <50% of the baseline level.

was no statistically significant difference between the treatment groups (table II).

Symptoms of Liver Failure

Significantly more patients in the TCR group than in the Ade-SD_4 group continued to experience fatigue after 7 days' treatment (47 *vs* 29% of patients, respectively; p = 0.004) and 14 days' treatment (15 *vs* 7%, respectively; p = 0.04). The only noticeable difference in the incidence of jaundice was observed after 14 days of treatment, when significantly fewer patients in the Ade-SD_4 compared with the TCR group were affected (26 *vs* 40%, respectively; p = 0.01).

With respect to the other major symptoms of acute viral hepatitis, patients treated with Ade-SD_4 experienced significant benefits compared with TCR (table II). After 7 days' treatment, the incidence of nausea was reduced by 89% in the Ade-SD_4 group compared with 75% in the TCR group (p = 0.01). Similarly, patients in the Ade-SD_4 group had significantly less general discomfort (p = 0.05) and a lower incidence of anorexia (reduced by 80 *vs* 58%; p = 0.001) after 7 days' treatment. In addition, fewer patients in the Ade-SD_4 group than in the TCR group had urinary discoloration after 7 days (60 *vs* 74%, respectively; p = 0.02) and 14 days (23 *vs* 39%, respectively; p = 0.01). No statistically significant differences between treatments were observed for liver tenderness, hepatomegaly, pale stools, vomiting, diarrhoea or pruritus.

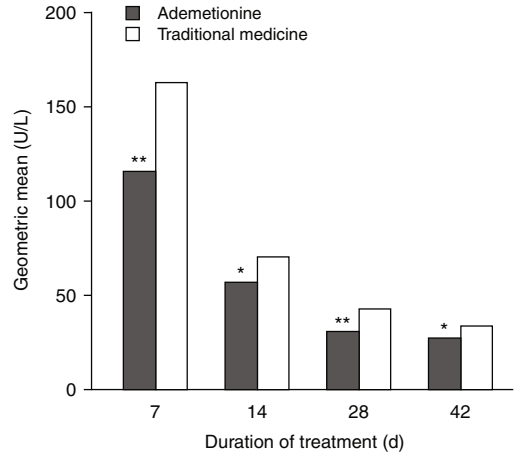

Fig. 3. Effects of ademetionine 1,4-butanedisulphonate or traditional Chinese medicine on serum glutamic pyruvic transaminase levels in patients with acute viral hepatitis associated with hepatocellular jaundice. The difference between treatments was set at * p < 0.05 and ** p < 0.01.

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Table II. Effect of ademetionine 1,4-butanedisulphonate (Ade-SD_4) or a traditional Chinese remedy (TCR) on efficacy variables in patients with acute viral hepatitis complicated by hepatocellular jaundice. Data are presented as the mean or frequency

Parameter	Ade-SD_4 a	TCR[a]
ALB (g/dl)		
Baseline	41.2 (21-59)	40.2 (23-53)
Day 42	43.8** (30-89)	43.6** (29-92)
ALP (U/L)		
Baseline	162.5 (64-335)	184.5 (51-471)
Day 42	83.4** (17-186)	92.3** (21-278)
TSBA (μg/dl)		
Baseline	220.9 (2-3250)	405.0 (5-4109)
Day 42	49.2** (2-890)	96.2** (1-1230)
γ-GT (U/L)		
Baseline	198.6 (12-752)	188.8 (26-973)
Day 42	70.1** (12-436)	69.9** (9-405)
PT (sec)		
Baseline	13.7 (11-35)	13.7 (10-19)
Day 42	13.4* (3-30)	12.8** (11-18)
PT (%)		
Baseline	95.2 (70-120)	86.2 (51-143)
Day 42	96.1 (70-119)	95.6* (59-142)†
Hepatomegaly (cm)		
Baseline	1.6 (0.5-6)	1.8 (1-13)
Day 42	0.9 (0.5-1)	1.0 (0.5-2)
General discomfort (score unit)		
Baseline	13 (4-20)	13 (4-19)
Day 42	3.4 (1-14)	3.6 (1-10)
Urinary discoloration		
Day 0	109	108
Day 42	6 (6)[b]	5 (5)[b]
Stool paleness		
Day 0	7	7
Day 42	0	0
Nausea		
Day 0	98	86
Day 42	1 (1)[b]	0
Vomiting		
Day 0	57	59
Day 42	1 (2)[b]	0
Diarrhoea		
Day 0	11	10
Day 42	0	0
Anorexia		
Day 0	99	89
Day 42	1 (1)[b]	0
Liver tenderness		
Day 0	51	53
Day 42	15 (29)[b]	15 (28)[b]
Scratching lesions		
Day 0	5	2
Day 42	0	0

a Values in parentheses are range of data unless otherwise stated.
b Values in parentheses are percentage.
ALB = serum albumin; **ALP** = serum alkaline phosphatase; **PT** = prothrombin time; **TSBA** = total serum bile acids; **γ-GT** = γ-glutamyl transferase.
Difference between baseline within treatment groups at the level of * $p \leq 0.01$ and ** $p = 0.001$. Difference between treatments at the level of † $p = 0.05$.

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Tolerability

Both Ade-SD_4 and TCR were well tolerated following oral and intravenous therapy. Only two adverse events were deemed severe in intensity: both were associated with phlebitis and considered possibly or probably related to Ade-SD_4 treatment. Of the remaining ten adverse events reported in the Ade-SD_4 group, eight were also considered possibly or probably related to study medication.

Haematological variables at the end of the study were similar in the two treatment groups. No significant differences in urinary protein, glucose, bilirubin or haemoglobin levels were observed between the treatment groups. However, in the Ade-SD_4 group the proportion of patients with bilirubin in their urine progressively decreased from 83% at baseline to 24% after 14 days and to 5% by the end of the study.

Discussion

Acute viral hepatitis is a systemic infection targeting the liver. Hepatitis A (HAV) and E (HEV) viruses are enterically transmitted (oral–faecal route) and cause acute self-limiting disease.

Although acute viral hepatitis (types A and E) generally resolves favourably, it is a disabling disease that often requires hospitalisation and prolonged absence from work, and consequently has a high socioeconomic cost, especially in countries where the disease is hyperendemic, such as China.

Treatments capable of reducing or alleviating the symptoms or shortening the course of the disease are required. Traditional remedies have been extensively used to treat liver disease in China. Data from experimental models of liver damage have demonstrated that TCR significantly reduces serum AST, ALT, STB and ALP levels, thereby supporting their clinical use.[2-4] However, the use of TCR in Western countries is limited as the pharmaceutical composition of such remedies is often poorly specified and supporting scientific literature in the English language is limited.

Based on the available evidence, Tanshinone, which is a derivative of phenanthrene-quinone isolated from *Salvia miltiorrhiza,* was selected for use in this study. Tanshinone may improve serum liver markers and reduce hepatomegaly, as it is known to inhibit DNA synthesis, fibrosis and cellular growth.[20-23] Similarly, Capillarin (the second component of the combination) reportedly improves serological status and stimulates bilirubin glucuronyl transferase activity, thereby improving the biochemical parameters of jaundice.[24-26] Furthermore, both Tanshinone and Capillarin are known to scavenge free radicals, inhibit lipid peroxidation, and stimulate cellular antioxidant enzymes, thereby providing further possible mechanisms for the treatment of liver disease.[21,27-32]

Ademetionine has also been shown to resolve liver damage and hepatocellular jaundice in experimental models. Furthermore, clinical studies support these findings and demonstrate that ademetionine is an effective treatment for hepatocellular jaundice associated with acute hepatitis.[33] Adachi and colleagues reported that oral ademetionine (600 mg/day) was as effective as oral prednisolone (30 mg/day initially, decreasing to 10 mg/day) at reducing serum bilirubin levels in patients with acute or chronic hepatitis complicated by intrahepatic cholestasis.[34] A subsequent study, in which patients with acute hepatitis complicated by intrahepatic cholestasis received ademetionine 800 mg/day intravenously for 2 weeks and were then randomised to receive either oral ademetionine 1600 mg/day or placebo for 2 months, demonstrated that treatment with oral ademetionine rather than placebo improved serum measures of hepatic function by approximately two-fold.[18] Furthermore, serum STB, SCB and transaminase levels in the placebo group were significantly worse at the end of the study compared with baseline. A placebo-controlled study with ademetionine (500 mg/day intravenously) in patients with acute hepatitis showed a marked fall in serum transaminase levels and a more rapid improvement in symptoms with ademetionine compared with placebo.[19]

The anticholestatic action of ademetionine involves two reactions: transmethylation and

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trans-sulphuration. Methylation of liver phospholipids in the plasma membrane of hepatocytes improves membrane fluidity, thereby improving bile secretion. The trans-sulphuration action of ademetionine replenishes the antioxidant status of the cell by increasing intracellular levels of thiol agents, such as cysteine, taurine and glutathione,[35] which protect against oxidative stress. Indeed, taurine plays a significant role in hepatocellular jaundice as taurine deficiency has been linked to the accumulation of toxic bile acids in hepatocytes.[36]

The present study compared the efficacy and tolerability of Ade-SD_4 with that of TCR in improving the biochemical parameters, as well as the subjective and objective symptoms, of acute viral hepatitis with associated hepatocellular jaundice. The study demonstrated that Ade-SD_4 was more effective than TCR in improving the biochemical markers of hepatic disease (STB, SCB and ALT) at all timepoints. Ade-SD_4 also had significant benefits over TCR at specific timepoints with respect to major symptoms of acute viral hepatitis, such as fatigue, jaundice and general discomfort. Furthermore, patients showed a more rapid biochemical response to treatment with Ade-SD_4 than to TCR. Finally, this study demonstrated that Ade-SD_4, administered intravenously for the first 2 weeks then orally for the next 4 weeks, was generally well tolerated in patients with acute viral hepatitis with associated hepatocellular jaundice.

Conclusion

The results of the present study provided further support for the clinical use of Ade-SD_4 in the treatment of liver disease complicated by hepatocellular jaundice. In addition, the data indicated that Ade-SD_4 has the potential to improve the symptoms of acute viral hepatitis with hepatocellular jaundice and to reduce the recovery time from acute hepatitis infection.

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References

1. Ockner RK. Acute viral hepatitis. In: Wyngaarden JB, Smith Jr LH, Bennett JC, editors. Cecil's Textbook of Medicine. 19th ed. Philadelphia: Saunders, 1992: 763-71
2. Tsai CC, Kao CT, Hsu CT, et al. Evaluation of four prescriptions of traditional Chinese medicine: syh-mo-yiin, guizhi-fuling-wan, shieh-qing-wan and syh-nih-sann on experimental acute liver damage in rats. J Ethnopharmacol 1997; 55: 213-22
3. Tsai CC, Kao ST, Hsu CT, et al. Ameliorative effect of traditional Chinese medicine prescriptions on alpha-naphthyl-isothiocyanate and carbon-tetrachloride induced toxicity in rats. Am J Chin Med 1997; 25: 185-96
4. Lin SC, Lin CC, Lu FJ, et al. Protective and therapeutic effects of huanglian-jie-du-tang on hepatotoxin-induced liver injuries. Am J Chin Med 1996; 24: 219-29
5. Cantoni GL. Biological methylation: selected aspects. Ann Rev Biochem 1975; 44; 435-51
6. Chawla RK, Lewis FW, Kutner MH, et al. Plasma cysteine, cystine, and glutathione in cirrhosis. Gastroenterology 1984; 87: 770-6
7. Arias IM. Mechanisms and consequences of ion transport in the liver. In: Popper H, Schaffner F, editors. Progress in liver diseases. New York: Grune & Stratton, 1986: 145-59
8. Boelsterli UA, Rakhit G, Balazs T. Modulation of S-adenosyl-L-methionine of hepatic Na^+, K^+-ATPase, membrane fluidity, bile flow in rats with ethynylestradiol-induced cholestasis. Hepatology 1983; 3: 12-7
9. Vendemiale G, Altomare E, Trizio T, et al. Effects of S-adenosyl-L-methionine on hepatic glutathione in patients with liver disease. Scand J Gastroenterol 1989; 24: 407-15
10. Martín-Duce A, Ortiz P, Cabrero C, et al. S-adenosyl-L-methionine synthetase and phospholipid methyltransferase are inhibited in human cirrhosis. Hepatology 1988; 8: 65-8
11. Bonfirraro G, Chieffi O, Quinti R, et al. S-adenosyl-L-methionine (SAMe)-induced amelioration of intrahepatic cholestasis of pregnancy. Results of an open study. Clin Drug Invest 1990; 2: 125-8
12. Frezza M, Surrenti C, Manzillo G, et al. Oral S-adenosyl-methionine in the symptomatic treatment of intra-hepatic cholestasis. A double-blind, placebo-controlled study. Gastroenterology 1990; 99: 211-5
13. Frezza M, Centini G, Cammareri G, et al. S-adenosylmethionine for the treatment of intrahepatic cholestasis of pregnancy. Results of a controlled clinical trial. Hepatogastroenterology 1990; 37 Suppl. 2: 122-5
14. Frezza M, Pozzato G, Chiesa L, et al. Reversal of intrahepatic cholestasis of pregnancy in women after high dose S-adenosyl-L-methionine administration. Hepatology 1984; 4: 274–8
15. Almasio P, Bortolini M, Pagliaro L, et al. Role of S-adenosyl-L-methionine in the treatment of intrahepatic cholestasis. Drugs 1990; 40 Suppl. 3: 111-23
16. Qin B, Guo S, Zhao Y, et al. A trial of ademetionine in the treatment of intrahepatic biliary stasis viral hepatitis. Zhonghua Gan Zang Bing Za Zhi 2000; 8: 158-60
17. Catalino F, Scarponi S, Cesa F, et al. Efficacy and safety of intravenous S-adenosyl-L-methionine therapy in the manage-

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ment of intrahepatic cholestasis of pregnancy. Clin Drug Invest 1992; 4: 78-82
18. Manzillo G, Piccinino F, Surrenti C, et al. Multicentre double-blind placebo-controlled study of intravenous and oral S-adenosyl-l-methionine (SAMe) in cholestatic patients with liver disease. Clin Drug Invest 1992; 4 Suppl. 4: 90-100
19. Botero RC, Delgado C. Placebo controlled trial of intravenous adenosylmethionine (SAMe) in patients with acute hepatitis A, B and NANB [abstract]. Hepatology 1991; 14: 199A
20. Liu J, Shen HM, Ong CN. *Salvia miltiorrhiza* inhibits cell growth and induces apoptosis in human hepatoma HepG(2) cells. Cancer Lett 2000; 153: 85-93
21. Li CX, Li L, Lou J, et al. The protective effects of traditional Chinese medicine prescription han-dan-gan-le, on CCl4-induced liver fibrosis in rats. Am J Chin Med 1998; 26: 325-32
22. Ryu SY, Lee CO, Choi SU. *In vitro* cytotoxicity of tanshinones from *Salvia miltiorrhiza*. Planta Med 1997; 63: 339-42
23. Wang X, Yuan S, Wang C. A preliminary study of the anti-cancer effect of tanshinone on hepatic carcinoma and its mechanism of action in mice. Zhonghua Zhong Liu Za Zhi 1996; 18: 412-14
24. Yin J, Wennberg RP, Miller M. Induction of hepatic bilirubin and drug metabolizing enzymes by individual herbs present in the traditional Chinese medicine, yin zhi huang. Dev Pharmacol Ther 1993; 20: 186-94
25. Zhang BZ, Ding F, Tan LW. Clinical and experimental study on yi-gan-ning granule in treating chronic hepatitis B. Zhongguo Zhong Xi Yi Jie He Za Zhi 1993; 13: 597-9
26. Chen Z. Clinical study of 96 cases with chronic hepatitis B treated with jiedu yanggan gao by a double-blind method. Zhong Xi Yi Jie He Za Zhi 1990; 10: 71-4
27. Ng TB, Liu F, Wang ZT. Antioxidative activity of natural products from plants. Life Sci 2000; 66: 709-23
28. Niu XL, Ichimori K, Yang X, et al. Tanshinone II-A inhibits low density lipoprotein oxidation in vitro. Free Radic Res 2000; 33: 305-12
29. Chu CY, Tseng TH, Hwang JM, et al. Protective effects of capillarisin on tert-butylhydroperoxide-induced oxidative damage in rat primary hepatocytes. Arch Toxicol 1999; 73: 263-8
30. Zhou GY, Zhao BL, Hou JW, et al. Protective effects of sodium tanshinone IIA sulphonate against adriamycin-induced lipid peroxidation in mice hearts in vivo and in vitro. Pharmacol Res 1999; 40: 487-91
31. Cao EH, Liu XQ, Wang JJ, et al. Effect of natural antioxidant tanshinone II-A on DNA damage by lipid peroxidation in liver cells. Free Radic Biol Med 1996; 20: 801-6
32. Zhao BL, Jiang W, Zhao Y, et al. Scavenging effects of *Salvia miltiorrhiza* on free radicals and its protection for myocardial mitochondrial membranes from ischemia-reperfusion injury. Biochem Mol Biol Int 1996; 38: 1171-82
33. Lieber CS, Williams R. Recent advances in the treatment of liver diseases. Drugs 1990; 40: 1-138
34. Adachi Y, Nanno T, Kanbe A, et al. The effects of S-adenosyl-L-methionine on intrahepatic cholestasis. Jap Arch Int Med 1986; 33: 185-92
35. Marchesini G, Bugianesi E, Bianchi G, et al. Effect of S-adenosyl-L-methionine administration on plasma levels of sulfur-containing amino acids in patients with liver cirrhosis. Clin Nutr 1992; 11: 303-8
36. Heaton KW. Bile salts. In: Wright R, editor. Liver and biliary disease. Eastbourne (UK): Bailliere Tindall, 1985

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