

# Comparison of long lasting therapeutic effects between succimer and penicillamine on hepatolenticular degeneration \*

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**Subject headings** hepatolenticular degeneration/  
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## Abstract

**AIM** To compare the long-term effect of succimer (Suc) with that of penicillamine (Pen) in treating hepatolenticular degeneration (HLD).

**METHODS** One hundred and twenty patients with HLD were divided into 2 groups. Group A ( $n=60$ ) received Suc 750mg, po. bid. Group B ( $n=60$ ) received Pen 250mg, po. qid. The period of maintenance treatment varied from 6 months to 3 years, averaging 1.5 years. Symptoms and therapeutic effects were evaluated by modified Goldstein scale.

**RESULTS** The total effectiveness of group A in two different periods of treatment were 80% and 85% respectively, higher than those of group B (58% and 59% respectively) ( $P<0.05$ ). Suc also had obvious curative effects for the patients who failed in the use of Pen. There were fewer side effect in group A than in group B ( $P<0.05$ ). Suc and Pen could increase urinary copper excretion effectively and continually.

**CONCLUSION** Suc is more effective and safer than Pen. Clinically, it can replace Pen as first-choice drug for long-term maintenance therapy of HLD.

## INTRODUCTION

Hepatolenticular degeneration (HLD) is an autosomal recessive disorder that causes changes in the basal ganglia and liver that respectively lead to neuropsychiatric disease, hepatitis and cirrhosis. The patients with HLD have to receive life long decoppering therapy, otherwise the disease will run an invariably fatal course. Penicillamine (Pen) has remained the treatment of first choice for more than forty years because it is readily available and of proven efficacy in some patients. However, the use of this drug is associated with a wide range of toxic reactions and unsatisfactory curative effect for the patients with hepatic type<sup>[1]</sup>. We have used succimer (Suc) to treat HLD since 1990, with satisfactory results. The short-term therapeutic effect of Suc is much better than that of Pen<sup>[2]</sup>. But no study has been carried out to investigate the long-term curative effects of these two copper-binding agents. Our study is to further investigate the long-term therapeutic effects of Suc and Pen.

## MATERIAL AND METHODS

### Subjects

One hundred and twenty patients with HLD were chosen for this study. They were definitely diagnosed after Feb. 1994 and reexamined in our institute from Jan. 1996 to Dec. 1997. They were divided into group A (Suc therapy) and group B (Pen therapy). Based on clinical symptoms, they were classified as neurological type (including Wilson type and pseudosclerosis type) and hepatic type<sup>[3]</sup>. The severity of disease was graded from I to V according to the modified Goldstein method<sup>[4]</sup>. These two groups were comparable for their age, sex, course of disease, period of treatment, clinical classification and severity (Table 1).

### Therapeutic methods

All patients had accomplished synthetical copper-binding therapy with unithiol or EDTA before they started long-term maintenance treatment with Suc or Pen. The period of maintenance treatment varied

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from 6 months to 3 years, averaging 1.5 years. The patients of group A were given Suc that was produced by Shanghai Xinya Pharmaceutical Plant. Each pill contains 0.25g mese DMSA. Oral dosage was 20 mg/kg - 30 mg/kg body weight, and administered twice daily. The patients of group B were given Pen produced by Shanghai Xinyi Pharmaceutical Plant. Oral dosage was 20mg/kg-30mg/kg body weight and administered 4 times daily. Considering that both Suc and Pen could chelate other trace and macro-elements in the process of copper-binding, especially zinc element, two hours after taking Suc or Pen, all patients of two groups were given 560mg zinc gluconate. Meanwhile, they were advised to take a copper-poor diet throughout the course of treatment and have their haemogram examined once a week. When patients were reexamined, their clinical conditions were independently judged by two experienced neurologists in our institute. Their haemogram, hepatorenal function, urinary trace and macro-elements were rechecked and compared with previous results. For the patients who did not obtain any effect from treatment, we asked to reexamine 2 months after they inter changed their copper-binding agents between group A and group B.

#### Therapeutic judgement criteria

**Marked effectiveness** Patient conditions were remarkably improved by two grades as compared with those before treatment.

**Improvement** Patient conditions were improved by one grade.

**Ineffectiveness or exacerbation** Patient conditions had no obvious change or became worse.

**Table 1 Characteristics of patients of group A and group B**

Characteristics	Group A (n=60)	Group B (n=60)
Mean age (yr)	20±4.0	18±5.0
Males/Females	34/26	31/29
Mean course of illness (yr)	2.5±2.0	3.0±1.0
Length of treatment		
6mon to 2yrs	40	38
>2yrs	20	22
Clinical classification		
Wilson type	24	26
Pseudosclerosis type	16	15
Hepatic type	10	9
Modified Goldstein Scale		
Grade I	15	18
Grade II	29	27
Grade III	10	11
Grade IV	6	4

## RESULTS

### Clinical effects

We investigated the curative effects of Suc and Pen on HLD in different periods of treatment. The results showed that the total effectiveness of group A was 80% and 85% respectively, higher than those of group B (58% and 59%,  $P<0.05$ ). Among 11 patients of group A who were demanded to replace Suc with Pen because of inefficiency of Suc, 1 (10%) was markedly improved and 2 (18%) improved, with an effectiveness rate of 27%. While in group B, 25 patients who changed to take Suc because of inefficiency of Pen, 5 (20%) were obviously improved, and 12 (48%) improved with an effectiveness rate of 68%. The difference was significant ( $\chi^2=5.1$ ,  $P<0.05$ , Table 2).

**Table 2 Comparison of long-term curative effect of Suc and Pen**

Group	Length of treatment	n	Markedly effective cases (%)	Improved cases (%)	Ineffective cases (%)	Total effective cases (%)
A	6mon to 2yrs	40	10(25)	22(55)	8(20)	32(80) <sup>a</sup>
	>2yrs	20	7(35)	10(50)	3(15)	17(85) <sup>a</sup>
B	6mon to 2yrs	38	5(15)	17(45)	16(42)	22(58)
	>2yrs	22	3(14)	10(45)	9(41)	13(59)

<sup>a</sup> $P<0.05$ , compared with group B.

**Table 3 Urinary trace and macro-elements changes after Suc and Pen therapy ( $\bar{x}\pm s$ )**

Group	Time	n	Copper ( $\mu\text{mol/L}$ )	Zinc ( $\mu\text{mol/L}$ )	Calcium (mmol/L)
A	Before treatment	60	4.4±2.9	4.3±2.5	1.3±0.4
	After treatment	60	19±6.0 <sup>b</sup>	21±7.3 <sup>b</sup>	1.8±0.6
B	Before treatment	60	4.1±2.6	4.7±2.5	1.3±0.4
	After treatment	60	20±6.0 <sup>b</sup>	20±6.9 <sup>b</sup>	1.8±0.5

<sup>b</sup> $P<0.01$ , compared with pre-treatment.

### Side effects

During the period of maintenance treatment, 9 patients (15%) in group A suffered from gingival suffusion and nosebleeding, rash and mild abdominal distension; 22 patients (37%) in group B mainly manifested with high temperature, rash and cytopenia. In both group A and B, there were 5 (5/9) and 16(16/22) patients who had the above side effects from 6 months to 2 years. These side effects could be abated or stopped after the patients were given haemostatic, leukocyte-increasing drugs and antiallergics. No patient in both groups had to stop his treatment because of side effects. The incidence of side-effects in group A was notably lower than in group B, the difference being statistically significant ( $\chi^2=7.36$ ,  $P<0.01$ ).

### Laboratory studies

Long-term copper-binding treatment, remarkably increased the urinary copper and zinc excretion ( $P < 0.01$ ), indicating that both Suc and Pen could effectively facilitate urinary copper and zinc excretion (Table 3). In group B, the white blood counts of patients were decreased, but there was no statistical significance compared with the results of pre-treatment, and no significant changes in hepatorenal function either.

### DISCUSSION

HLD is an autosomal recessive inheritant disease, abnormalities in serum ceruloplasmin, urinary copper excretion and copper accumulation in the liver have for many years suggested a primary defect in copper metabolism as the cause. By now, the gene responsible for HLD was located in chromosome 13q14.3, encoding a P-type ATPase. At least 70 different mutations have since been described in this copper-ATPase gene in individual with HLD<sup>[5]</sup>. Long-term anticopper therapy is necessary for patients to maintain their normal life. All neurologists considered Pen as a drug of first choice before Suc was clinically adopted. Suc is a new broad spectrum heavy metal antidote with low toxicity and high water solubility. It is easily discharged through urine after taken orally. We began to use Suc to cure HLD in 1990 and found that it could improve effectively neurologic symptoms and facilitate evidently biliary copper excretion besides increasing clearly urinary copper excretion<sup>[6,7]</sup>.

Comparing the long-term therapeutic effects between Suc and Pen on HLD, we found that Suc was Superior to Pen ( $P < 0.05$ ) because the former caused clinical symptoms to exacerbate less frequently than the latter did. Suc also had obvious curative effects for the patients who failed in Pen treatment. Side effects incidence of Suc was obviously lower than that of Pen ( $P < 0.01$ ). Laboratory results showed that long-term use of Suc or Pen could increase effectively urinary copper and zinc excretion ( $P < 0.01$ ). As Suc has better short- and long-term therapeutic effects, less side effects and permanent urinary copper excretion function, we recommend that Suc should be used as a drug of first choice in long-term maintenance therapy of HLD.

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