Clinical efficacy of combined sodium dimercaptopropanesulfonate and zinc treatment in neurological Wilson's disease with D-penicillamine treatment failure

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Abstract

Objectives: There are limited pharmacological treatments for patients with neurological Wilson's disease (WD) and a history of copper-chelating treatment failure.

Methods: We retrospectively evaluated the clinical records of 38 patients with WD who were treated with sodium dimercaptopropanesulfonate (DMPS) and zinc (group 1) or zinc alone (group 2). All patients had a history of neurological deterioration during their previous treatment with D-penicillamine (DPA).

Results: Twenty-one patients were treated with intravenous DMPS for 4 weeks, followed by zinc gluconate for 6 months, and the treatment protocol was repeated twice. Relative to the baseline, repeated DMPS therapy and zinc maintenance therapy decreased neurological scores continuously ($p < 0.01$). Sixteen patients (76.2%) demonstrated neurological improvements after 1 year of therapy and four patients (19.0%) exhibited neurological deterioration at the follow-up session. In addition, 17 patients were treated with zinc monotherapy for 12 months. Two patients (11.8%) demonstrated neurological improvements and five patients (29.4%) exhibited neurological deterioration. Compared with the patients in group 2, a greater improvement ratio ($p < 0.01$) and lower deterioration ratio ($p < 0.01$) were observed in the patients in group 1 after 1 year of therapy.

Conclusions: Our findings indicate that the safety and efficacy of combined treatment of DMPS and zinc is superior to those of zinc monotherapy in patients with neurological WD with a history of DPA treatment failure.

Keywords: copper, neurological deterioration, sodium dimercaptopropanesulfonate, Wilson's disease, zinc

Introduction

Wilson's disease (WD) is an autosomal recessive disease caused by a mutation in the *ATP7B* gene. The disease leads to copper accumulation in various tissues and organs, predominantly in the liver, brain, cornea, and kidneys [Ala *et al.* 2007].

WD treatment can be divided into two stages: initial therapy to eliminate excess copper in symptomatic patients and lifelong maintenance therapy to reduce copper level as well as prevent copper reaccumulation. Chelators such as D-penicillamine (DPA) and trientine are recommended as initial therapies for WD since they can induce a negative copper balance by cupriuresis [Roberts and Schilsky, 2008]. However, DPA can exacerbate neurological symptoms of patients with WD [Brewer *et al.* 1987]. Trientine has a similar propensity to penicillamine in causing neurologic deteriorations [Brewer *et al.* 2006]. Further, the high cost and limited supply of trientine has restricted its use in developing countries. Treatment with common chelating agents for neurological WD is somewhat controversial. Zinc confers a moderate

anticopper effect, and is recommended as a maintenance therapy [Roberts and Schilsky, 2008]. Zinc monotherapy appears to be effective and safe in neurologic WD and may have a role as a first-line therapy in patients with neurological disease. However, worsening of symptoms has been reported with zinc treatment in WD [Weiss *et al.* 2011; Merle *et al.* 2007]. The current guidelines of the European Association for Study of the Liver (EASL) recommend that the initial treatment of symptomatic WD should include a chelating agent [EASL, 2012].

Sodium 2,3-dimercapto-1-propane sulfonate (DMPS), first synthesized by Petrunkin in 1956 [Petrunkin, 1956], is an intravenous copper-chelating agent that forms complexes with various heavy metals. DMPS combines with copper ions to form a thiol compound, which is excreted by the kidneys [Hol *et al.* 2003; Wang *et al.* 2003]. In China, DMPS is routinely employed for the treatment of copper accumulation in WD [Wang *et al.* 2003; Xu *et al.* 2013] and it is considered as an alternative treatment for patients with WD who are intolerant to oral DPA. However, limited studies have evaluated the efficacy and safety of combined treatment of DMPS and zinc in patients with WD and a history of DPA-induced neurological deterioration.

In the present study, 38 patients with WD with a history of DPA-induced neurological exacerbation received combined treatment of DMPS and zinc, or zinc alone, and the clinical outcomes were examined. The aim of the study was to elucidate the more effective therapeutic therapy for patients with WD with a history of DPA treatment failure.

Methods

Clinical data of 38 patients with WD were retrospectively analysed. The study included patients with WD, referred to the clinics of the First Affiliated Hospital of Sun Yat-Sen University between 2009 and 2013. Diagnosis of WD was based on the clinical manifestations. The minimal diagnostic criteria for the neurological form of WD were typical neurological symptoms, low ceruloplasmin, and elevated urine copper levels.

The study was approved by the ethics committee of Sun Yat-Sen University. From the medical records, the following data were obtained: medical and family history and clinical examination results such as neurological assessments, brain magnetic resonance imaging (MRI), indicators of liver failure, and the presence or absence of a Kayser–Fleischer ring observed through a slit lamp. Neurological functioning was evaluated using the neurological subscale of a global assessment scale (GAS), which assesses different aspects of neurological dysfunction caused by WD [Aggarwal *et al.* 2009].

All patients had histories of DPA treatment and experienced exacerbation of neurological symptoms during their previous DPA treatment. The patients were divided into two groups. Patients in group 1 were hospitalized and were intravenously administered DMPS at an initial dose of 5–10 mg/kg. The initial dose was rapidly adjusted to 15–20 mg/kg over the first 2–3 days of treatment and the dose was subsequently maintained throughout the course of the treatment [Xu *et al.* 2013]. Each treatment course consisted of DMPS therapy for 5 consecutive days, followed by a withdrawal period of 2 days to promote tolerance. The neurological status was evaluated using the GAS for WD. During the last course of therapy, zinc gluconate was added for transition to maintenance therapy. For older children and adults, 150 mg/day was administered in three divided doses. For children under the age of 15, a dose of 75 mg/day was administered in three divided doses. After 6 months of maintenance therapy, the patients received repeated DMPS therapy for 4 weeks, were subjected to zinc monotherapy for 6 months, and were monitored. The patients in group 2 received outpatient treatment of zinc only and were followed for 1 year. Patients were generally re-examined at 6 months and 1 year following the commencement of zinc therapy.

The results were expressed as the mean ± SD or the median and range, as indicated. The findings were analysed by t tests for unpaired quantitative data (two tailed) and χ^2 tests for qualitative data. Statistical analyses were performed using the IBM Statistical Product and Service Solutions (SPSS) software, version 19.0. p values up to 0.05 were considered significant.

Results

Group 1 (n = 21) consisted of 13 male and 8 female patients, and group 2 (n = 17) consisted of 11 male and 6 female patients. All patients showed neurological symptoms, including dysarthria, dysphagia, salivation, dystonia, tremor,

Table 1. Clinical data of 38 patients with Wilson's disease with neurological deterioration during DPA treatment.

	Group 1	Group 2
Patients (*n*)	21	17
Age at onset (range, median)	18.9 ± 9.8	20.5 ± 11.2
Mean duration of illness (months)	18.6 ± 35.2	26.2 ± 43.8
CP (mg/dl)	7.0 ± 2.0	7.0 ± 3.0
Kayser–Fleischer ring (*n*)	19	14
With neurologic symptoms (*n*)	21	17
With psychiatric symptoms (*n*)	4	3
With liver disease (*n*)	18	15
With splenomegaly (*n*)	15	11
Abnormal brain MRI (*n*)	21	17
Duration of DPA treatment (months)	3.9 ± 2.7	3.7 ± 3.4
Dose of DPA (mg/day)	125~750	125~750

CP, ceruloplasmin; DPA, D-penicillamine; MRI, magnetic resonance imaging.

Parkinsonism, and abnormal posture and gait. Four patients in group 1 and three patients in group 2 demonstrated predominant psychiatric or behavioural manifestations. MRIs of the brain indicated abnormality in all symptomatic patients. Signal abnormalities were noted on T1-W and T2-W images in the basal nuclei, thalamus, brain stem, cerebellum, brain cortex, and white matter. Signs of liver dysfunction including jaundice, aminotransferase elevation, cirrhosis, and splenomegaly were observed. Low serum ceruloplasmin levels and high 24 h urine copper levels were found in all patients of both groups prior to treatment. Patient characteristics prior to therapy are summarized in Table 1.

Table 2 shows the levels of serum and urine copper during therapy, relative to baseline. Serum copper levels did not differ significantly from baseline levels in either group. It was observed that 24 h urine copper levels significantly increased after 2 weeks ($p < 0.01$) and decreased after 4 weeks of DMPS therapy. The 24 h urine copper levels did not differ significantly from baseline in group 2 patients.

The neurological outcomes of patients over time are shown in Table 3. Compared with baseline, the neurological scores of group 1 patients decreased slightly after 4 weeks of DMPS therapy and continued to decrease after 6 months of zinc monotherapy ($p < 0.05$). Repeated DMPS therapy and zinc maintenance therapy decreased neurological scores continuously, relative to baseline ($p < 0.01$). Consistent with the neurological scores, eight patients (38.1%) demonstrated neurological improvements after DMPS therapy and the number of patients increased to 12 (57.1%) after 6 months of zinc therapy. Relative to baseline, 16 of the 21 patients (76.2%) in group 1 demonstrated neurological improvement at the 1-year follow up. The results indicated that DMPS was more effective in reducing tremor, Parkinsonism, and posture and gait disorders than was zinc monotherapy. Three patients (14.3%) presented with neurological deterioration after 4 weeks of DMPS therapy and the neurological scores of these patients did not recover to baseline after two treatment courses of DMPS combined with zinc. Dystonia, speech, and swallowing dysfunctions were more likely to deteriorate than other symptoms. One patient demonstrated deterioration during the first course of zinc monotherapy and did not recover before the end of the follow-up period. It was noted that the patient did not follow a low-copper diet according to the doctor's advice, which may have contributed to neurological deterioration. Compared with baseline, a slight increase in neurological scores was observed during zinc monotherapy (group 2). Two patients (11.8%) exhibited neurological improvements and five patients exhibited neurological deterioration after 1 year of zinc monotherapy, as indicated by an increase of 1~2 points on the GAS. As stated above, after 1 year of therapy, the improvement ratio of group 1 was significantly greater than that of group 2 ($p < 0.01$), and the deterioration ratio was lower than that of group 2 ($p < 0.01$).

Table 2. Serum copper and 24 h urine copper in 38 patients with Wilson's disease during treatment.

Group		First course			Second course			1 year
		Baseline	2 weeks	4 weeks	6 months	2 weeks	4 weeks	
1	**Serum copper**	0.24 ± 0.04	0.23 ± 0.03	0.20 ± 0.05	0.23 ± 0.06	0.23 ± 0.08	0.21 ± 0.08	0.20 ± 0.04
	Urine copper	156.7 ± 121.9	1149.7 ± 202.9**	856.3 ± 312.7**	131.3 ± 89.5	1084.7 ± 393.6**	712.4 ± 451.9**	119.3 ± 78.5
	Patients (*n*)	21	21	21	21	21	21	21
2	**Serum copper**	0.25 ± 0.06			0.24 ± 0.04			0.22 ± 0.07
	Urine copper	163.7 ± 1054			121.1 ± 77.4			131.9 ± 93.5
	Patients (*n*)	17			17			17

Serum copper (mg/liter); urine copper (μg). First course: sodium dimercaptopropanesulfonate and zinc; second course: zinc.
* $p < 0.05$; ** $p < 0.01$.

Table 3. Neurologic outcomes using the GAS scoring system in patients with Wilson's disease during the treatment.

Group		Baseline	4 weeks	6 months	4 weeks	1 year
1 (*n* = 21)	**Scores**	13.4 ± 5.6	12.2 ± 4.7	11.8 ± 5.3*	11.2 ± 5.1**	10.7 ± 4.3**
	Improvement (*n*, %)		8 (38.1)	12 (57.1)	14 (66.7)	16 (76.2)
	Deterioration (*n*, %)		3 (14.3)	4 (19.0)	4 (19.0)	4 (19.0)
2 (*n* = 17)	**Scores**	14.2 ± 6.1		14.4 ± 6.3		14.9 ± 6.7
	Improvement (*n*, %)			1 (5.9)		2 (11.8)
	Deterioration (*n*, %)			4 (23.5)		5 (29.4)

* $p < 0.05$; ** $p < 0.01$.

Myelosuppression was observed in 11 patients during DMPS therapy (Table 4) and all of these patients had splenomegaly. The blood counts of the majority of patients remained stable following dose reduction and an improvement in leukopenia and thrombocytopenia was observed after 6 months of zinc therapy.

Of the 18 patients with liver disease in group 1, transaminase levels were mildly elevated during the first course of DMPS therapy ($p < 0.05$) (Table 4). Transaminase levels remained stable in the majority of patients and declined after two courses of zinc therapy ($p < 0.01$). Further, the transaminase levels of 15 patients with liver disease in group 2 were significantly elevated during zinc monotherapy ($p < 0.05$).

None of the patients demonstrated abnormalities in serum albumin or bilirubin during DMPS or zinc therapy. Additionally, obvious fluctuations in routine urine, creatinine, or blood urea nitrogen were not observed in any patients during the treatment period.

Discussion

The present study found that combined treatment of DMPS and zinc improved neurological symptoms in the majority of patients with WD with exacerbated neurological symptoms during previous DPA treatment. Of the patients in group 1, 76.2% showed gradual neurological improvement during combination therapy, while 11.8% of patients in group 2 exhibited neurological improvements after 1 year of zinc monotherapy. These findings indicate that DMPS and zinc combination therapy was more effective than zinc monotherapy in patients with neurological WD and DPA-induced neurological deterioration. Further, improvements in neurological functioning were observed during the post-DMPS zinc therapy period in patients subjected to combination therapy; while neurological functioning did not significantly improve in patients treated with zinc alone. Additionally, a significant increase in urine copper levels was observed during DMPS treatment. This indicates that the copper-chelating effect of initial DMPS therapy was necessary for positive neurological outcome. We hypothesize

Table 4. Blood count and liver function tests in patients with Wilson's disease.

	Baseline	2 weeks	4 weeks	6 months	2 weeks	4 weeks	1 year
Mean blood counts in 11 patients in group 1 who showed myelosuppression during DMPS treatment							
HGB (g/liter)	122.6 ± 11.8	123.1 ± 13.4	122.9 ± 13.7	123.6 ± 10.9	122.5 ± 9.2	126.1 ± 11.7	125.3 ± 13.4
WBC ($\times 10^9$/liter)	4.2 ± 1.5	3.7 ± 1.3	3.3 ± 1.9	4.0 ± 1.6	3.7 ± 1.5	3.4 ± 1.7	4.1 ± 1.8
PLT ($\times 10^9$/liter)	79.7 ± 39.1	61.1 ± 31.2	51.5 ± 22.8	71.4 ± 22.7	62.8 ± 21.3	60 ± 27.2	76.1 ± 34.8
Mean values of liver function tests of 18 patients in group 1 with liver disease							
ALT (U/liter)	51.3 ± 17.8	54.4 ± 21.4	56.2 ± 20.9*	46.6 ± 12.1*	49.3 ± 14.5	47.2 ± 17.6	37.2 ± 16.4**
AST (U/liter)	44.8 ± 14.5	46.2 ± 13.2	48.8 ± 16.3*	42.5 ± 14.5*	41.2 ± 15.4	40.6 ± 13.7	34.7 ± 17.8**
ALB (g/liter)	42.4 ± 5.7	43.9 ± 4.7	40.2 ± 6.8	43.7 ± 3.2	41.8 ± 4.9	42.3 ± 6.3	40.1 ± 5.2
Bilirubin (μmol/liter)	13.7 ± 9.3	14.4 ± 6.4	13.1 ± 7.1	14.0 ± 7.8	14.8 ± 4.4	14.3 ± 5.3	12.2 ± 4.1
Mean values of liver function tests of 15 patients in group 2 with liver disease							
ALT (U/liter)	44.5 ± 15.3			47.5 ± 17.4*			51.3 ± 26.4*
AST (U/liter)	43.2 ± 14.1			44.7 ± 13.3			47.5 ± 10.6*
ALB (g/liter)	41.4 ± 4.8			40.5 ± 7.2			39.0 ± 5.3
Bilirubin (μmol/liter)	16.1 ± 5.6			14.9 ± 6.2			15.9 ± 4.7

*$p < 0.05$; **$p < 0.01$.
ALB, albumin; ALT, alanine transaminase; AST, aspartate aminotransferase; HGB, haemoglobin; PLT, platelet; WBC, white blood cell.

that the relatively rapid reduction of deposited copper induced by DMPS may compensate for the inability of zinc maintenance therapy to control copper loading.

The exact mechanism in which DPA and trientine result in worsening of neurological symptoms is unclear. However, a likely explanation is that the mobilization of large copper reservoirs in the liver and/or the brain leads to elevation of copper levels in the brain. Previous studies have reported that DPA therapy combined with cupric sulphate resulted in the production of reactive oxygen species within cells [Gupte and Mumper, 2007a, 2007b]. Therefore, this mechanism may be involved in DPA-induced neurological decline. It is difficult to explain the positive impact of DMPS on neurological symptoms in our study compared with that of DPA. Similar studies on DMPS and trientine have not been reported, and it is consequently unclear whether a similar cytotoxicity occurs in cells during treatment with DMPS or trientine with copper.

The present study found that 19.0% of patients experienced worsening of symptoms after 1 year of combination therapy and 29.4% demonstrated symptom exacerbation with zinc monotherapy. This finding indicates that DMPS is probably more effective as an initial therapy than zinc monotherapy in slowing the progression of WD. Zinc induces the synthesis of metallothionein in the enterocytes, which binds to copper in the enterocyte and prevents copper absorption [Brewer, 1999]. This anticopper mechanism promotes a longer duration for zinc to elicit protective effects in WD, and the disease may therefore progress during the prolonged period of copper toxicity. We propose that zinc monotherapy was not adequate to prevent the progression of neurological WD symptoms in the present study. The current guidelines of the European Association for the Study of the Liver [EASL, 2012] and the American Association for the Study of Liver Diseases (AASLD) stated that initial treatment of symptomatic patients with WD should include a chelating agent (DPA or trientine) [Roberts and Schilsky, 2008]. Considering the findings of previous studies [Brewer *et al.* 1987, 2009], the deterioration rate (19%) observed in our study was not remarkable. However, taking into account the history of neurological deterioration of the patients in this study, chelating treatment was relatively effective in controlling neurological symptoms. It appears that DMPS therapy is more effective as an initial therapy than zinc monotherapy for patients with WD who experienced DPA-induced neurological deterioration. It should be noted that all patients in this study had a history of DPA treatment failure; thus, it is not a representation of all patients with WD, and further studies are required. In the present study, zinc was administered at an adult dose of 50 mg three times daily as recommended by the AASLD guidelines. Hoogenraad and colleagues used a higher zinc loading dose (67.5 mg and 90 mg three times daily) for WD treatment [Hoogenraad *et al.* 1987], but the safety and compliance were not fully discussed. Besides, serum and urine zinc tests, which assess the adherence to zinc treatment, were not included in the follow-up-index, which may affect the overall strength of the results. However, adherence to medicine and subsequent visits indicate patients were compliant with treatment.

Adverse effects of DMPS have previously been reported, including myelosuppression and transiently raised serum alanine aminotransferases [Wang *et al.* 2003; Xu *et al.* 2013]. In the present study, myelosuppression primarily occurred during DMPS therapy in patients with splenomegaly. Leukopenia or thrombocytopenia can be alleviated by dosage adjustment in most cases. Therefore, low-dose DMPS treatment may be safer for patients with WD and splenomegaly. The moderate elevation in transaminase levels observed in this study was consistent with the findings of a recent study conducted in China [Xu *et al.* 2013]. Further, the majority of patients in this study did not require DMPS dose adjustments.

Conclusions

The present study demonstrated the efficacy of combination therapy of DMPS and zinc for the treatment of neurological symptoms in patients with WD with a history of neurological deterioration, and suggests that initial DMPS therapy followed by zinc maintenance may improve neurological symptoms in patients with WD with DPA treatment failure, relative to zinc monotherapy. A limitation of DMPS treatment is that intravenous administration is inconvenient for long-term treatment. In the absence of DMPS, zinc can control the progression of neurological symptoms, albeit at a slower rate.

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Conflict of interest statement

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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