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ORIGINAL ARTICLE

Prospective Pilot Study of a Single Daily Dosage of Trientine for the Treatment of Wilson Disease

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Abstract
Background Wilson disease requires lifelong therapy, currently given daily in multiple divided dosages.
Aim To prospectively evaluate once-daily trientine as therapy for Wilson disease.
Methods Study group: eight patients (seven males) aged 22–71 years with stable Wilson disease treated from 4 to 50 years. Patients were monitored for 3 months then for 12 months on a single daily dose of trientine (15 mg/kg).
Results All patients remained clinically well. ALT and AST fluctuated in some, but none required treatment stoppages or side effects. Liver synthetic function was unchanged. Mean 24-h urine copper and zinc excretions at end of treatment were 313.4 ± 191.7 and $2{,}214 \pm 1{,}346$ μg, respectively.
Conclusions Once-daily trientine should be explored further for possible maintenance therapy for WD. Single daily dose may improve adherence to therapy. Larger trials and longer-term follow-up will establish the safety and treatment efficacy of this once-daily treatment regimen for WD (registration: NCT01472874).

Keywords Wilson disease · Treatment · Trientine · Adherence

Abbreviations

ALT	Alananine aminotransferase
AST	Aspartate aminotransferase
INR	International normalized ratio
WD	Wilson disease

Introduction

Wilson disease (WD) is an autosomal recessive disorder of copper metabolism affecting ~1:30,000 individuals [1, 2]. Liver and neurological injury may be prevented or treated by lifelong medical therapy with D-penicillamine or trientine, or zinc salts that inhibit copper absorption. Up to 50 % of WD patients have medication non-adherence [3]. Failure to adhere to treatment inevitably leads to neurological injury and psychiatric symptoms, hepatic failure, and ultimately death [4].

Trientine was approved for WD patients intolerant of D-penicillamine [5, 6]. Trientine is gaining popularity as a first-line agent due to its favorable safety profile. Trientine is conventionally dosed at 750–1,500 mg/day in 2–4 divided doses. Increases in urinary trientine excretion correlate with increased urinary copper excretion [7].

There have been very few prospective studies for treating WD. Weiss et al. [8] retrospectively reviewed treatments for WD, concluding that zinc was less effective than chelating

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agents for long-term use. They observed discontinuation for treatment failure for 14/88 on zinc compared to 4/213 on chelation therapy. Important factors such as having to interrupt daily routines to avoid taking medications with food is a significant lifestyle issue for some patients and important for maintaining medication adherence [9].

Once-daily dose yields the highest compliance for drugs with average tolerability; the more often a drug is taken, the less the adherence [10, 11]. Adherence is better for drugs perceived as having life and death consequence such as critical antiarrhythmic therapy [12]. Drug adherence is more problematic for asymptomatic or stable conditions such as hypertension or maintenance therapy for WD [13, 14]. Daily dosed medications available as long-acting preparations are frequently utilized in the treatment of chronic medical disorders such as hypertension [15]. These daily dosed medications had better adherence. There are currently no comparable extended release preparations for treatments for WD.

There are few investigations of available chelators for WD to inform about the frequency of their administration [16]. Conventional recommendations are multiple daily dosages administered apart from meals to enhance intestinal absorption and maximize copper excretion. The potential benefits of a once-daily trientine dose as maintenance therapy for WD were previously reported as a retrospective review of case reports [17]. Three patients took trientine once-daily for 2–15 years. Liver function and parameters of copper metabolism were normal, and examinations showed clinical stability. These data suggested the need for a prospective trial. To this end, we undertook a prospective study to determine the safety and effectiveness of a 12-month course of a once-daily weight-based dose of trientine for maintenance treatment for WD.

Methods

We designed a prospective study of once-daily trientine for WD. The protocol was approved by the HIC committee at Yale University Medical Center. The trial was registered on www.clinicaltrials.gov (registration number NCT01472874, first received: November 11, 2011, last updated: July 17, 2012). Inclusion criteria required a diagnosis of WD, >1 year clinical stability on current therapy, and stable liver disease. The study group included eight patients (seven males) aged 22–71 years treated from 4 to 50 years (median of 8 years). Presentations of WD included asymptomatic ($n = 1$), incidental detection of KF rings ($n = 1$), neuropsychiatric then liver and stable neurological disease ($n = 1$), stable neurological with liver disease ($n = 1$) and liver disease alone ($n = 4$). Prior treatments were zinc acetate ($n = 2$), D-penicillamine ($n = 1$), and trientine ($n = 5$). Patients were consented before entry into the clinical trial. Three consecutive monthly clinical and laboratory evaluations were made before beginning the study treatment. The physical evaluations included assessments of the neurological and liver disease. Patients were asked to complete a pre- and post-study questionnaire. Serum and 24-h basal urinary studies prior to entry included blood counts with platelets, ALT, AST, ALP, total bilirubin, direct bilirubin, gamma glutamyl transpeptidase, albumin, international normalized ratio (INR), serum copper, serum ceruloplasmin, antinuclear antibody, erythrocyte sedimentation rate, 24-h urine for copper and zinc excretion and volume, urinalysis, AST-to-platelet ratio [18], and levels of several proteins important for liver fibrosis [19]. Statistical testing of data was performed using Student's t test (two tailed) compared mean values obtained before and after treatment.

Treatment was with trientine, 15 mg/kg (rounded upward to the nearest 250 mg) once-daily for 12 months. Patients were monitored monthly for 3 months and at 6, 9, and 12 months, and study coordinators reviewed patient logs and conducted formal pill counts. Treatment dose was based on AASLD practice guidelines and represents the dosage used in children [1, 20, 21]. Subjects were to be removed from the study if the laboratory values were abnormal (ALT or AST > twice baseline values) for two sequential blood tests or for any decline in the patient's health.

Results

After treatment with once-daily trientine, all were clinically well. Their physical examination remained unchanged, and no new neurological signs were detected. There were no stoppages of treatment or dropouts from the study.

Liver Function Tests, Copper and Zinc Studies

Results for ALT, AST, total bilirubin, INR, albumin, serum copper, 24-h urine copper and zinc are shown in Table 1. ALT and AST levels were not statistically changed by treatment in 6/8 patients, and mean values were 41.38 ± 31.81 and 28.22 ± 10.57 U/L, respectively, on their prior therapy, and 50.89 ± 32.29 and 33.53 ± 11.17 U/L at trial end. In two (patients 2 and 3), the differences in mean ALT before and after treatment did reach statistical significance, but end of treatment values were at the upper limit of normal in one and above normal but <2 times the upper limit of normal in the other. Neither had changes in hepatic synthetic function or bilirubin over the course of treatment. Total bilirubin, albumin, and INR were relatively unchanged for the cohort at the trial end. Urinary copper excretion increased from baseline values from 2.8 to 9.5 times baseline values in patients changed from pre-treatment zinc to trientine as expected, but

Table 1 Biochemical testing before and after trientine treatment

	Medication	Pre-treatment		Post-treatment		*p* value
		Mean ± SD	Min–max	Mean ± SD	Min–max	
ALT (0–35 U/L)						
P1	Trientine	33.33 ± 4.04	31–38	58.66 ± 15.84	40–82	0.123
P2	D-Penicillamine	16.75 ± 2.21	14–19	34 ± 4.77	28–41	**0.006**
P3	Zinc	29.75 ± 5.56	26–38	52.67 ± 16.35	37–76	**0.003**
P4	Trientine	17.75 ± 2.5	15–21	22.17 ± 4.44	19–31	0.242
P5	Zinc	35.25 ± 23.64	17–69	19.2 ± 2.16	17–22	0.311
P6	Trientine	100.75 ± 30.99	58–132	116.16 ± 12.73	102–139	0.483
P7	Trientine	22.5 ± 2.08	20–25	26.67 ± 6.56	18–38	0.659
P8	Trientine	73 ± 13.68	57–89	72.33 ± 6.37	64–80	0.955
All		41.38 ± 31.81	14–132	50.89 ± 32.29	17–139	0.448
INR (0.8–1.15)						
P1	Trientine	0.95 ± 0.03	0.93–0.99	1.05 ± 0.05	0.99–1.13	0.129
P2	D-Penicillamine	1.12 ± 0.05	1.05–1.17	1.24 ± 0.04	1.18–1.31	**0.038**
P3	Zinc	0.94 ± 0.02	0.93–0.95	1.04 ± 0.03	1.01–1.09	**0.019**
P4	Trientine	0.90 ± 0.02	0.88–0.94	0.96 ± 0.06	0.89–1.09	0.086
P5	Zinc	1.01 ± 0.05	0.98–1.1	1.03 ± 0.02	0.99–1.07	0.706
P6	Trientine	1 ± 0.04	0.96–1.05	1.03 ± 0.01	1.02–1.06	0.114
P7	Trientine	0.99 ± 0.04	0.95–1.05	1.04 ± 0.04	0.99–1.12	0.071
P8	Trientine	0.99 ± 0.02	0.95–1.01	1.02 ± 0.07	0.96–1.16	0.289
All		0.99 ± 0.07	0.93–1.17	1.05 ± 0.08	0.89–1.31	**0.002**
Cu serum (0.75–1.45 mcg/ml)						
P1	Trientine	0.74 ± 0.07	0.66–0.81	0.79 ± 0.05	0.71–0.87	0.297
P2	D-Penicillamine	0.29 ± 0.01	0.27–0.31	0.26 ± 0.02	0.24–0.3	**0.048**
P3	Zinc	1.0 ± 0.07	0.94–1.1	0.88 ± 0.10	0.8–1.02	0.062
P4	Trientine	0.65 ± 0.04	0.6–0.7	0.66 ± 0.01	0.64–0.69	0.533
P5	Zinc	0.48 ± 0.59	0.4–0.53	0.43 ± 0.06	0.38–0.53	0.434
P6	Trientine	0.11 ± 0.02	<0.1–0.14	0.11 ± 0.008	0.11–0.13	0.634
P7	Trientine	0.80 ± 0.06	0.74–0.9	0.84 ± 0.02	0.82–0.85	0.474
P8	Trientine	0.16 ± 0.02	0.13–0.19	0.16 ± 0.009	0.15–0.18	0.717
All		0.54 ± 0.30	<0.1–1.1	0.52 ± 0.30	0.11–1.02	0.964
Cu urine (15–60 mcg/24 h)						
P1	Trientine	144.3 ± 9	135–154	239.8 ± 90.3	150–411	0.301
P2	D-Penicillamine	843.5 ± 35.9	793–877	485.6 ± 276.4	131–833	0.084
P3	Zinc	181.7 ± 34.8	144–224	513.5 ± 166.4	267–684	**0.033**
P4	Trientine	60.2 ± 40.7	18–116	200 ± 33.5	155–234	0.028
P5	Zinc	10 ± 1.4	9 and 11	95.2 ± 20.5	66–122	0.052
P6	Trientine	327 ± 27.3	303–363	374 ± 113.9	203–476	0.625
P7	Trientine	227.6 ± 33.7	189–251	370.8 ± 86.6	227– 450	0.104
P8	Trientine	318.7 ± 154.4	135–507	211.8 ± 144.5	110–500	0.445
All		287.9 ± 259.1	9–877	313.4 ± 191.7	66–833	0.643
Zn urine (300–600 mcg/24)						
P1	Trientine	1,109 ± 86	944–1,311	1,944 ± 1,110	820–2,917	0.442
P2	D-Penicillamine	3,297 ± 106	3,192–3,439	3,441 ± 1,645	1,481–5,228	0.855
P3	Zinc	1,990 ± 493	1,475–2,535	1,718 ± 799	727–3,091	0.969
P4	Trientine	1,598 ± 566	912–2,297	2,669 ± 642	1,986–3,671	0.155
P5	Zinc	656 ± 186	503–864	1,316 ± 209	963–1,461	0.113
P6	Trientine	1,482 ± 322	1,002–1,698	1,231 ± 461	498–1,759	0.432

Table 1 continued

	Medication	Pre-treatment		Post-treatment		*p* value
		Mean ± SD	Min–max	Mean ± SD	Min–max	
P7	Trientine	3,607 ± 377	3,172–3,844	4,251 ± 784	2,892–4,837	0.405
P8	Trientine	1,805 ± 737	764–2,503	1,336 ± 1,054	691–3,453	0.644
All		1,959 ± 1,003	503–3,844	2,214 ± 1,346	498–5,228	0.428
Albumin (3.5–5.0 g/dL)						
P1	Trientine	4.4 ± 0.2	4.2–4.6	4.53 ± 0.18	4.3–4.8	0.789
P2	D-Penicillamine	0.29 ± 0.01	0.27–0.31	0.26 ± 0.02	0.24–0.3	**0.048**
P3	Zinc	1.0 ± 0.07	0.94–1.1	0.88 ± 0.10	0.8–1.02	0.062
P4	Trientine	0.65 ± 0.04	0.6–0.7	0.66 ± 0.01	0.64–0.69	0.533
P5	Zinc	0.48 ± 0.59	0.4–0.53	0.43 ± 0.06	0.38–0.53	0.434
P6	Trientine	0.11 ± 0.02	0.1–0.14	0.11 ± 0.008	0.11–0.13	0.634
P7	Trientine	0.80 ± 0.06	0.74–0.9	0.84 ± 0.02	0.82–0.85	0.474
P8	Trientine	0.16 ± 0.02	0.13–0.19	0.16 ± 0.009	0.15–0.18	0.717
All		0.54 ± 0.30	0.1–1.1	0.52 ± 0.30	0.11–1.02	0.964

Bold values are statistically significant ($p < 0.05$)

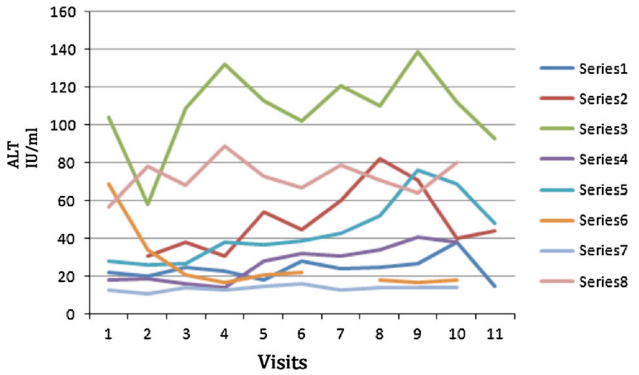

Fig. 1 The graph demonstrates the variation of ALT during the period of the experimental study. Visits 1–4 were the pre-treatment and baseline visits. With upper limit of normal at 40, only 3 were above at the start. All the patients had end values below the 0 time point at the end of the study except series 3 but that patient had a value below 100 a year later

was relatively unchanged for patients on D-penicillamine or trientine following their change to once-daily trientine. One patient, patient 4, had a 330 % increase in copper excretion, likely from better adherence. In line with the findings obtained from urinary copper, the patients all had non-ceruloplasmin copper that was below 15 mcg/dl prior to study entry and no patient exceeded this threshold during the study. Mean 24-h urine zinc excretion was not significantly changed after treatment for the cohort, but there were two patients on trientine that increased their zinc excretion by ~40 % (Fig. 1).

Full Blood Count, ANA, and Dropout from the Study

Blood counts remained stable after therapy (data not shown), and all had negative screens for antinuclear antibodies before and after treatment. There was no patient dropout from the trial, and no patients were removed from the study for abnormal laboratory values or clinical evidence of worsening disease.

Indirect Measures of Hepatic Fibrosis

The AST-to-platelet ratio did not change at treatment end (data not shown), and similarly, serum markers associated with fibrosis (that are also components of the Fibrotest™) remained similar or improved from before to end of treatment (see Table 2).

Questionnaires

Questionnaire results are shown in Table 3. Before the study, three patients missed one dose/week; one each missed 2, 4, and 5 doses/week, and two missed >5 doses/week. At study end, all patients reported that the once-daily dose of the trientine improved their ability to avoid missing medication dosages and that it was easier and preferable to take the medication once-daily.

Discussion

WD is treated with chelators to promote copper excretion, or with zinc to reduce copper absorption. There is no preferred treatment regimen given the lack of prospectively controlled studies to estimate the relative treatment efficacy or adherence to the available treatments for WD. Unfortunately, the lifelong need for therapy and requirement for

Table 2 Serum fibrosis markers

	Medication	Alpha-2-macroglobulin		Haptoglobin		Apolipoprotein A1		GGT		Total bilirubin		ALT	
		Start	End	Start	End	Start	End	Start	End	Start	End	Start	End
P1	Trientine	23		159	156	167	168	36	52	0.62	0.3	31	40
P2	D-Penicillamine	269	264	<6.0	<6.0	161	178	42	48	1.06	1.47	14	38
P3	Zinc	565	443	89.9	60	145	180	17	32	0.38	0.47	38	69
P4	Trientine	177	191	86	95.9	169	196	13	14	0.32	0.34	17	22
P5	Zinc	208	181	155	271	171	134	27	18	0.38	0.32	17	18
P6	Trientine	353	397	12.6	7.5	174	157	66	100	0.8	0.65	132	112
P7	Trientine	208	188	117	126	130	103	27	31	0.92	0.47	23	27
P8	Trientine	149	143	128	121	111	108	90	105	0.96	0.58	89	80

Units and ranges of normal for tests are as follows: alpha-2-macroglobulin: 131–293 mg/dL; haptogloblin: 20–200 mg/dL; apolipoprotein A1: 94–178 mg/dL; GGT: 11–55 U/L; total bilirubin: <1.2 mg/dL; ALT: 0–34 U/L

Table 3 Questionnaire responses at start and end of study

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Pre-treatment questionnaire								
What medication are you taking for Wilson's disease?	Trientine	D-Pen	Zinc	Trientine	Zinc	Trientine	Trientine	Trientine
How long have you been on this medication?	3 years	40 years	5 years	5.5 years	3 years	4.3 years	5 years	5.25 years
How many times per day do you take your medication?	2	1	2	2	3	2	2	2
How many dosages of your medication are taken 1 h before or 2 h after meals?	All	All	All	All	1	All	All	All
How many dosages of your medication do you miss in a week's time?	1	1	>5	1	>5	2	5	4
What is the longest time you have gone without your medication?	1 day	2 days	4 days	30 days	4 days	0	4 days	300 days
Does having to take the medication 1 h before meals or 2 h after meals interfere with your daily schedule?	Yes	No	No	No	Yes	Yes	No	Yes
Do you think it will be easier for you to take your medication as a single dosage?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Post-treatment questionnaire								
Did taking your medication as a single daily dosage improve your ability to take the entire daily amount of medication needed?	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Was taking your medication as a single daily dosage less interfering with your daily schedule?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Would you prefer to take your medications as a single daily dosage if your testing showed that your Wilson disease was well controlled during this trial?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Which medication would you prefer to take for your Wilson disease?	Zinc*	Trientine	Trientine	Trientine	Trientine	Trientine	Trientine**	Trientine

* Financial consideration; ** whichever is "cheapest"

multiple daily dose of medications has led to non-adherence to treatment and clinical deterioration and death for some WD patients, leading us to look for alternatives.

Trientine is increasingly recognized as first-line treatment for WD due to fewer unwanted effects than D-penicillamine. Pancytopenia occurs rarely, and hypersensitivity

reactions and renal effects have not been reported [22]. Neurological deterioration during initiation of therapy is infrequent but recognized [23]. Therefore, we focused our attention on this agent.

In this prospective pilot study, we evaluated once-daily trientine for WD maintenance therapy. Our expectations of continued clinical and laboratory stability were mostly achieved. There were mild changes in serum aminotransferases in the group overall as reflected by the ranges noted in Table 1, but liver function (INR, and albumin and total bilirubin) remained mostly unchanged (Table 1). In two (patients 2 and 3, Table 1) in whom ALT levels increased slightly at study end, we found no obvious reason for this observation. Their exams, weight, and hepatic synthetic function remained intact. Patient 3 missed >5 doses a week prior to the study, and his increased urine copper excretion probably reflected consistent medication usage. In the study group, there were two patients in whom past symptoms included neurological and psychiatric symptomatology, but in one of these individuals the psychiatric symptoms were resolved, and in both neurological symptoms were stable. Both had been maintained on therapy with stable examinations prior to the study, as was a requirement for inclusion in the study, and remained stable throughout the study.

Urine copper excretion and serum copper were stable for patients before and during the study (Table 1), including the "free" non-ceruloplasmin copper and urinary copper. The patients all had non-ceruloplasmin copper that was below 15 mcg/dl prior to entry into the study, and no patient exceeded this threshold during the study (data not shown). Liver biopsies were not obtained, as they are not routinely used to follow treatment in WD. However, AST-to-platelet ratio and serum markers of fibrosis were not changed at study end, indirectly suggesting no change in hepatic fibrosis.

Zinc must be taken apart from meals for WD treatment and is often administered thrice daily [24]. The normative requirement for absorbed zinc is set at 1.4 mg/day for men and 1.0 mg/day for women. All patients had elevated urine excretion of zinc while on trientine. To our knowledge, there is no evidence for zinc deficiency in WD patients on therapy with trientine or D-penicillamine, likely due to the ubiquitous presence of dietary zinc. Activity of alkaline phosphatase, a zinc dependent enzyme, was not altered in our patients who transitioned from zinc to trientine (data not shown).

Patient questionnaires revealed a perceived advantage of trientine given once-daily was the convenience of not having to time dosages to 1 h before or 2 h after meals. The once-daily regimen seemed to improve patient adherence to treatment, in particularly in the two patients who missed >5 doses/week before the study. Though we cannot negate the effect of study enrollment on adherence since patients had medication checks and periodic pill counts, we hoped that once-daily treatment would improve adherence beyond the study period.

We believe that once-daily weight-based dose of trientine merits further study for long-term maintenance therapy for WD. Of note, the pediatric weight-based dosage often exceeds what is given to adults on a daily basis. The choice of dose in adults is empiric and based on treatment experience of experts as there is a lack of evidence-based comparative data on this subject. The weight-based dose used in this study compared to the usual one-size fits all dose deserves particular mention and highlights the need for more formal studies to determine the proper dose of these medications. In our cohort, the patients previously on chelation therapy maintained similar 24-h urine copper excretions in the study, suggesting the 15 mg/kg yields adequate daily copper excretion. We do recognize the limitation of having not studied more than one dosage, and this can be addressed in future studies.

Since the study group was small in this pilot study, a larger study group would be required to achieve statistical significance to prove efficacy and bioequivalence. We believe that the time to detect signal for treatment failure or non-adherence is within 6 months based on prior studies of adolescents who were non-adherent with treatment [8], and is consistent with our personal experience with a large number of patients with Wilson disease over the years. Based on this, current recommendations are for bi-annual monitoring of patients in maintenance therapy in both AASLD and EASL guidelines [1, 26]. If we had seen lower urine copper excretion, then this might lend credence to the suggestion for potential for slow copper accumulation, but it is important that we did not observe this at all. Therefore, while longer periods of study are always wished for, we believe our period of observation exceeded the minimum needed to detect signal for treatment failure or non-adherence.

Our observations suggest that a once-daily weight-based dosage of trientine is an attractive regimen for WD patients for maintenance therapy. A recent publication of from Dzieżyc et al. [25] reported improved survival rates for asymptomatic patients adherent to therapy compared to non-compliant patients, further strengthening the argument that a simpler treatment regimen will benefit adherence. Longer-term follow-up of our patients and others on once-daily therapy is needed to establish its safety and treatment efficacy, with promising implications for the future management of patients with WD.

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Conflict of interest None.

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