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Withdrawal of penicillamine from zinc sulphate–penicillamine maintenance therapy in Wilson's disease: Promising, safe and cheap

S. Sinha *, A.B. Taly

National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore - 560 029, India

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Abstract

Background: Penicillamine, once considered the cornerstone of treatment for Wilson disease (WD), is rather expensive and toxic, and often causes neurological worsening. Zinc sulphate, aiming at the treatment of free-copper toxicosis, has emerged as effective, safe and cheap alternative.
Aim: To assess the effect of withdrawal of penicillamine from maintenance treatment with penicillamine and zinc sulphate.
Patients and methods: 45 patients of WD (M:F: 28:17; age at diagnosis: 13.5±63 years), on both penicillamine (P) and zinc sulphate (Zn), couldn't continue penicillamine due to financial constraints. Their clinical data, disability and impairment scores (Schwab and England (S&E) score, Neurological Symptom Score (NSS), and Chu staging) and follow-up data of patients maintained only on zinc sulphate were recorded.
Results: Majority of patients (84.4%) had neuropsychiatric manifestations. The mean duration of treatment with penicillamine (P) and zinc sulphate (P+Zn), before stopping penicillamine, was 107.4±67.3 months. 40 patients improved variably, while the rest didn't. They received only zinc sulphate for 27.2±8.5 months (range: 12 to 34) and 44 patients (97.7%) remained status quo or improved marginally. Only one patient reported worsening in dysarthria. Their disability and impairment scores during combination (penicillamine and zinc sulphate) and Zn alone were: Chu (1.3±0.5 vs. 1.5±1.9; $p=0.4$), NSS (1.8±3.1 vs. 1.5±2.3; $p=0.03$) and S&E (96.4±5.6 vs. 98.6±3.5; $p=0.03$). There were no adverse effects.
Conclusions: Withdrawal of penicillamine from zinc sulphate/penicillamine maintenance therapy for patients with Wilson's disease was effective, safe and economic, for almost all patients. This retrospective study reiterates that zinc sulphate may be used as a preferred mode of treatment for patients with Wilson's disease.

Keywords: Penicillamine withdrawal; Treatment; Wilson disease; Zinc sulphate; Zinc therapy treatment of choice

1. Introduction

Wilson's disease (WD) is an inherited disease of copper metabolism caused by a failure of biliary excretion of excess copper. Accumulated copper causes liver disease in these patients, and in perhaps two thirds of patients, it causes brain damage leading to clinical neurologic or psychiatric dysfunction [1–4]. Maintenance treatment involves reversing the positive copper balance. There are many therapeutic approaches to manage these patients. Chelators like penicillamine or trientine induce negative copper balance by cupriuresis. There is high level of endogenous secretion of copper in alimentary canal. Zinc sulphate aims at treatment of copper toxicosis by blocking the absorption of copper and increase excretion in the stool [5–8]. The pivotal role of penicillamine in the management of WD has been a matter of debate for the past three decades. While it induces a negative copper balance, when given in the initial phase of the treatment, it causes worsening of neurological symptoms in about 10 to 50% of patients [9,10]. Further, in countries with limited resources, the cost of penicillamine for life-long use is rather prohibitive. It has taken many years before it became worldwide recognized that zinc sulphate therapy, aiming at

* Corresponding author. Tel.: +91 80 26995150; fax: +91 80 26564830.
E-mail addresses: sanjib_sinha2004@yahoo.co.in, sanjib_sinha@nimhans.kar.nic.in (S. Sinha).

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Table 1
Clinical and biochemical parameters on combination penicillamine+zinc sulphate and zinc sulphate alone therapy

Parameters	Baseline	P+Zn	Zn	Statistics
Disability and impairment scores				
Chu staging [a]	–	1.3±0.5	1.5±1.9	p=0.4 (2 tailed)
NS Score [a]	–	1.8±3.1	1.5±2.3	p=0.03 [a] (2 tailed)
S&E ADL [a]	–	96.4±5.6	98.6±3.5	p=0.03 [a] (2 tailed)
Biochemical abnormalities				
S. Copper (μg/dl)	N=45, 66.6±45.3	–	N=26, 65.7±31.7	p=0.84 (2 tailed)
S. Ceruloplasmin (mg/dl)	N=45, 10.5±9.1	–	N=29, 7.9±5.8	p=0.01 (2-tailed)
24-hour urine Cu (μg/24 h)	N=45, 448.6 ±508.9	–	N=17, 375.3±324.9	p=0.35 (2-tailed)

[a] See Appendix.

the treatment of copper toxicosis, is effective, safe and economic [5,6,10,11].

The aim was to study the effect of withdrawal of penicillamine from treatment, in patients with WD who were on maintenance therapy with combined treatment of penicillamine/zinc sulphate.

2. Patients and methods

A large cohort of patients with WD is being followed over the last three decades (1970–2003), at the Department of Neurology, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India, a University teaching hospital and a major referral center. These patients have been diagnosed, based on the clinical manifestations, low serum copper and ceruloplasmin levels, increased 24-hour urinary copper excretion and presence of KF ring by slit lamp examination. This retrospective study included forty five patients of WD, who were on regular combination de-coppering therapy with penicillamine (P) [250 mg capsules] and zinc sulphate (Zn) [220 mg capsules containing 50 mg elemental zinc, 1 h before food]. They had to stop penicillamine due to financial constraints. Subsequently these patients were only on zinc sulphate as maintenance treatment. The patients were followed up clinically with periodic biochemical tests. Facility to assess urinary zinc was not available.

Their demographic and clinical features, disability and impairment scores (Schwab and England (S and E) score, Neurological Symptom Score (NSS), and Chu staging: see Appendix) and follow-up data of patients maintained only on Zn sulphate were recorded. Data of pre-symptomatic subjects with WD were excluded from analysis.

3. Results

There were 28 males and 17 females. The mean age at onset of illness and diagnosis of these 45 patients was 12.8±5.9 years (range: 4 to 29.5 years) and 13.5±63 years (range: 4 to 30 years) respectively. Forty patients (88.8%) had neuropsychiatric manifestations while rest had hepatic form at onset of their illness.

The mean duration of treatment, on a combination of penicillamine and zinc (P+Zn), before stopping penicillamine was 107.4±67.3 months (range: 36 to 252 months). The dosages varied widely and ranged from 250 mg to 1000 mg/day of penicillamine and 1320 to 1980 mg/day in 3 divided dosages of zinc sulphate, 1 h before food (elemental zinc 300 to 450 mg). Forty patients had shown variable improvement while rest did not. After withdrawal of penicillamine these patients received zinc sulphate as the only maintenance therapy for a mean duration of 27.2±8.5 (range: 12 to 34 months). Among them, 44 patients (97.7%) remained status quo or improved marginally. Only one patient reported worsening in dysarthria, while on zinc.

The disability and impairment scores were documented when the patients were on treatment with penicillamine and zinc sulphate (P+Zn) and repeated while on zinc sulphate (Zn) alone during follow-up. Baseline scores were not available for analysis. The improvements in these scores are mentioned in Table 1 and the differences in the NSS (1.8±3.1 vs. 1.5±2.3; p=0.03) and S&E (96.4±5.6 vs. 98.6±3.5; p=0.03) were statistically significant. The biochemical parameters at baseline and while on zinc alone are also mentioned in the table.

In this retrospective study, there were no adverse effects reported with zinc alone. In India, zinc is cheaper than penicillamine. The cost of a capsule of 250 mg penicillamine is 13 INR i.e. (8.5 to 34.5 USD per month, depending on dosages), while the cost of one capsule of zinc sulphate (220 mg) is only 0.55 INR i.e. (2 to 3.3 USD per month, depending on dosages).

4. Discussion

This study strengthens the fact that zinc alone can be safely used in the treatment of WD. This study found that 45 patients continued to maintain improvement or remained stable for a minimum period of 2 to 3 years. The improvement in disability and impairment scores were statistically significant. The patients reported no major adverse effects, while on zinc sulphate alone. In 1961, Schouwink published his doctoral thesis on the influence of zinc supplementation in Wilson's disease [5]. Subsequently, Hoogenraad described the beneficial use of zinc sulphate in WD [6,7]. Brewer et al. in their series of 141 patients documented that zinc acetate was effective as a sole therapy in the long-term (10 years) maintenance

treatment of Wilson's disease and that it had a low toxicity [12,13]. Their results also demonstrated the efficacy of zinc acetate therapy in treating the pre-symptomatic patient from the beginning of therapy [14]. Ever since then zinc has gained wide acceptance. Compliance is a major problem in treating this disease over a long period of time. Zinc sulphate, being cheaper compared to penicillamine and zinc acetate, may have better compliance in poor patients. In India the price for zinc sulphate is about 24 to 40 USD/year, and penicillamine about 102 to 414 USD/year. In India zinc acetate is not available and therefore not prescribed in this cohort.

Walshe and Yealland [15] discussed their results of chelation treatment of 137 patients presenting with neurological Wilson's disease. They observed that 57 patients made an excellent response, 36 patients made a good recovery, but were left with some minor neurological deficit while 24 patients had a poor response and 20 had died – 11 had received adequate chelation while 9 had little or no treatment. [1,15]. Walshe proposed penicillamine as drug of choice [16]. But Brewer et al. reported that there was initial worsening following use of penicillamine and recommended against its use [10,17]. The authors believed that some of the newly acquired neurological deficit might not improve subsequently. This paradoxical worsening is not noted in patients on zinc therapy. In this retrospective study, worsening following penicillamine was not looked for and hence this aspect cannot be commented. In our earlier study we had recommended "start Low and go slow" approach for the use of penicillamine, based on the worsening noted following rapid escalation of penicillamine to maximum dose [18]. Veen et al. [19] had used zinc following deterioration with penicillamine [19]. It is noteworthy that irrespective of the mode of the treatment, compliance is of paramount importance [20].

Efficacy of oral zinc therapy in patients with Wilson's disease has been demonstrated by uptake of 64Cu and copper balance measurements. Yuzbasiyan-Gurkan et al. [21] in a study with 64Cu uptake measurements and concomitant intestinal biopsies investigated the relationship of reduced copper absorption to the levels of intestinal metallothionein in patients with Wilson's disease at different stages of zinc therapy. They detected pronounced increase in intestinal metallothionein levels and a sharp drop in 64Cu absorption, 4 to 5 days after the initiation of zinc treatment. Conversely, metallothionein levels decreased and 64Cu uptake increased on the discontinuation of zinc therapy [21]. In another study by Brewer et al. [10], 12 patients with WD, most of whom had received intensive treatment with penicillamine, were given zinc therapy as their sole medication for copper control. Serial liver biopsies after a follow-up period of 12- to 20-months did not reveal hepatic re-accumulation of copper during zinc therapy [22]. Copper balance, 24-hour urinary copper excretion, and non-ceruloplasmin plasma copper concentration all indicated good copper control during zinc therapy. High doses of zinc have been reported to cause elevated serum lipase, amylase and even lymphocytic dysfunction. But these have not been proven by well-designed studies [23–25]. The present study was retrospective in nature and did not systematically analyze these parameters. Nevertheless our patients did not report recurrent infections or clinical features of pancreatitis. Zinc is also safe in pregnancy [26,27].

The major limitation of the present study was the retrospective nature. The disability and impairment scores were not available at baseline. Similarly the biochemical assays were not performed when penicillamine was stopped and when they were on combination therapy. Withdrawal of penicillamine from zinc sulphate/penicillamine maintenance therapy for patients with Wilson's disease was effective, safe and economic, for almost all patients. This retrospective study reiterates that zinc sulphate may be used as a preferred mode of treatment for patients with Wilson's disease.

Appendix A

Chu Staging

Stage-I — Hand tremors, slurred speech or tendency to fall with minimal or no functional impairment.

Stage-II — Moderate rigidity or involuntary movements, unsteady gait, dysarthria, psychiatric symptoms or any combination of these.

Stage-III — Confined to bed or wheel chair with severe generalized rigidity or spasticity, gross ataxia or marked involuntary movements.

Neurological Symptom Score (NSS)

Speech (0–5)
Eye movements (0–3)
Sialorrhea (0–3)
Deglutation (0–4)
Bradykinesia (0–3)
Rigidity (0–3)
Dystonia (0–3)
Tremor (0–4)
Chorea (0–4)
Dysdiadokenesis (0–3)
Reflexes (0–2)
Plantars (0–1)
Postural instability (0–4)
Gait (0–4)
Total: 46

Schwab and England Activities of Daily Living (0–100%)

Rating can be assigned by rater or by patient.

- 100% — Completely independent. Able to do all chores without slowness, difficulty, or impairment.
- 90% — Completely independent. Able to do all chores with some slowness, difficulty, or impairment. May take twice as long.

- 80% — Independent in most chores. Takes twice as long. Conscious of difficulty and slowing
- 70% — Not completely independent. More difficulty with chores. Takes three to four times for some chores. May require large part of day for chores.
- 60% — Some dependency. Can do most chores, but very slowly and with much effort and errors, some impossible.
- 50% — More dependants. Help with half of the chores. Difficulty with everything.
- 40% — Very dependent. Can assist with all chores but can do few alone.
- 30% — With effort. Now and then does a few chores alone or begins alone. Much help needed.
- 20% — Nothing alone. Can do some slight help with some chores. Severely invalid.
- 10% — Totally dependant, helpless.
- 0% — Vegetative functions such as swallowing, bladder and bowel function are not functioning. Bedridden.

References

[1] Walshe JM. Wilson's disease. In: Vinken PJ, Bruyn GW, Klawans HL, editors. Handbook of clinical neurology, vol. 49. Amsterdam: Elsevier; 1986. p. 223–38.
[2] Brewer GJ, Yuzbasiyan-Gurkan V. Wilson disease. Medicine 1992;71:139–64.
[3] Brewer GJ. Wilson's disease. a clinician's guide to recognition, diagnosis and management. Boston: Kluwer Academic Publishers; 2001.
[4] Taly AB, Meenakshi-Sundaram S, Sinha S, Swamy HS, Arunodaya GR. Wilson disease: description of 282 patients evaluated over three decades. Medicine 2007;86(2):112–21.
[5] Schouwink G. De hepatocerebrale degeneratie, met een onderzoek naar de koperstofwisseling. University of Amsterdam MD thesis; 1961
[6] Hoogenraad TU, Van den Hamer CJ, Koevoet R, Korver EG. Oral zinc in Wilson's disease. Lancet 1978;2(8102):1262.
[7] Hoogenraad TU, Koevoet R, de Ruyter Korver EG. Oral zinc sulphate as long-term treatment in Wilson's disease (hepatolenticular degeneration). Eur Neurol 1979;18(3):205–11.
[8] Hoogenraad TU, Van Hattum J, Van den Hamer CJ. Management of Wilson's disease with zinc sulphate. Experience in a series of 27 patients. J Neurol Sci 1987;77(2-3):137–46.
[9] Scheinberg IH, Sternlieb I. Wilson's Disease. Wilson's disease. Philadelphia: WB Saunders; 1984.
[10] Brewer GJ, Terry CA, Aisen AM, Hill GM. Worsening of neurologic syndrome in patients with Wilson's disease with initial penicillamine therapy. Arch Neurol 1987;44:490–3.
[11] Hoogenraad TU. Paradigm shift in treatment of Wilson's disease: zinc therapy now treatment of choice. Brain Dev 2006;28(3):141–6.
[12] Brewer GJ, Dick RD, Johnson VD, Brunberg JA, Kluin KJ, Fink JK. Treatment of Wilson's disease with zinc: XV long-term follow-up studies. J Lab Clin Med 1998;132(4):264–78.
[13] Brewer GJ. Treatment of Wilson's disease with zinc. J Lab Clin Med 1999;134(3):322–4.
[14] Brewer GJ, Dick RD, Yuzbasiyan-Gurkan V, Johnson V, Wang Y. Treatment of Wilson's disease with zinc. XIII: Therapy with zinc in presymptomatic patients from the time of diagnosis. J Lab Clin Med Jun 1994;123(6):849–58.
[15] Walshe JM, Yealland M. Chelation treatment of neurological Wilson's disease. Q J Med 1993;86:197–204.
[16] Walshe JM. Penicillamine: the treatment of first choice for patients with Wilson's disease. Mov Disord 1999;14(4):545–50.
[17] Brewer GJ. Penicillamine should not be used as initial therapy in Wilson's disease. Mov Disord 1999;14(4):551–4.
[18] Prashanth LK, Taly AB, Sinha S, Ravishankar S, Arunodaya GR, Vasudev MK, et al. Factors that influence prognosis in severe forms of Wilson Disease. Q J Med 2005;98(8):557–63.
[19] Veen C, van den Hamer CJ, de Leeuw PW. Zinc sulphate therapy for Wilson's disease after acute deterioration during treatment with low-dose D-penicillamine. J Intern Med 1991;229(6):549–52.
[20] Hoogenraad TU. Dangers of interrupting de-coppering treatment in Wilson's disease. Arch Neurol 1994;51:972–3.
[21] Yuzbasiyan-Gurkan V, Grider A, Nostrant T, Cousins RJ, Brewer GJ. Treatment of Wilson's disease with zinc: X. Intestinal metallothionein induction. J Lab Clin Med 1992;120(3):380–6.
[22] Brewer GJ, Hill GM, Dick RD, Nostrant TT, Sams JS, Wells JJ, et al. Treatment of Wilson's disease with zinc: III. Prevention of reaccumulation of hepatic copper. J Lab Clin Med 1987;109(5):526–31.
[23] Brewer GJ, Johnson V, Kaplan J. Treatment of Wilson's disease with zinc: XIV. Studies of the effect of zinc on lymphocyte function. J Lab Clin Med 1997;129(6):649–52.
[24] Brewer GJ, Yuzbasiyan-Gurkan V, Johnson V. Treatment of Wilson's disease with zinc. IX: Response of serum lipids. J Lab Clin Med 1991;118(5):466–70.
[25] Yuzbasiyan-Gurkan V, Brewer GJ, Abrams GD, Main B, Giacherio D. Treatment of Wilson's disease with zinc. V. Changes in serum levels of lipase, amylase, and alkaline phosphatase in patients with Wilson's disease. J Lab Clin Med 1989;114(5):520–6.
[26] Sinha S, Taly AB, Prashanth LK, Arunodaya GR, Swamy HS. Successful pregnancies and abortions in symptomatic and asymptomatic Wilson's disease. J Neurol Sci 2004;217:37–40.
[27] Brewer GJ, Johnson VD, Dick RD, Hedera P, Fink JK, Kluin KJ. Treatment of Wilson's disease with zinc xvii: treatment during pregnancy. Hepatology 2000;31(2):364–70.