ORIGINAL CONTRIBUTION

Treatment of Wilson Disease With Ammonium Tetrathiomolybdate

III. Initial Therapy in a Total of 55 Neurologically Affected Patients and Follow-up With Zinc Therapy

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Background: It is unclear what anticopper drug to use for patients with Wilson disease who present with neurologic manifestations because penicillamine often makes them neurologically worse and zinc is slow acting.

Objective: To evaluate the frequency of neurologic worsening and drug adverse effects with ammonium tetrathiomolybdate.

Design: Open-label study of 55 untreated patients (22 of them new) presenting with neurologic Wilson disease treated with tetrathiomolybdate varying from 120 to 410 mg/d for 8 weeks and then followed up for 3 years. Neurologic function was assessed with scored neurologic and speech tests.

Setting: A university hospital referral setting.

Patients: All untreated, newly diagnosed patients with neurologic Wilson disease.

Intervention: Treatment with tetrathiomolybdate.

Main Outcome Measures: Neurologic function was evaluated by neurologic and speech examinations. Drug adverse effects were evaluated by complete blood cell counts and biochemical measures.

Results: Only 2 (4%) of 55 patients treated with tetrathiomolybdate showed neurologic deterioration, compared with an estimated 50% of penicillamine-treated patients. Five of the 22 new patients exhibited bone marrow suppression and 3 had aminotransferase elevations. These numbers are higher than in the original 33 patients and appear to be due primarily to a more rapid dose escalation.

Conclusions: Tetrathiomolybdate shows excellent efficacy in patients with Wilson disease who present with neurologic manifestations. With rapid escalation of dose, adverse effects from bone marrow suppression or aminotransferase elevations can occur.

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THE INITIAL TREATMENT of patients with Wilson disease who present with neurologic symptoms is problematic. Of the 3 commercially available anticopper agents, penicillamine often makes about half of these patients irreversibly neurologically worse,[1] trientine hydrochloride is untested but its actions are much like those of penicillamine, and zinc is too slow acting. To fill this therapeutic void, we have been developing ammonium tetrathiomolybdate.[2-4]

Tetrathiomolybdate acts differently than previous anticopper drugs. It forms a tripartite complex with copper and protein that is very stable.[5-8] Given with food, tetrathiomolybdate complexes food copper with food protein, rendering that copper, along with endogenously secreted copper in saliva, gastric juice, and intestinal secretions, unabsorbable. This puts the patient in an immediate negative copper balance. Given away from food, tetrathiomolybdate is absorbed into the blood and there complexes freely available and potentially toxic copper with blood albumin. This complexed copper cannot be taken up by cells and is therefore nontoxic.[8] The lightly bound and potentially toxic copper of organs is in equilibrium with that in the blood, and further copper toxicity in various organs in Wilson disease is quickly stopped, generally in 1 to 2 weeks, with tetrathiomolybdate therapy.

We have previously published 3 articles in this journal about the development of tetrathiomolybdate for this therapeutic purpose.[2-4] The most recent, in 1996,[4] presented data on 33 patients with neurologic presentations who were treated with tetrathiomolybdate up until that time. In this article, we present 22 additional pa-

Table 1. Initial Data on the New Sample of 22 Patients With Wilson Disease

Patient No./ Sex/Age, y	Hepatic Copper, µg/g	Urine Copper, µg/d	Treatment History (No. of Weeks)	Major Signs and Symptoms
169/F/25	NA	127	Penicillamine (1½)	Dysarthria, dystonia, severe chorea, nonambulatory
172/F/20	873	111	Zinc acetate (2)	Dysarthria, incoordination*
173/F/20	240	NA	Penicillamine (2)	Mild dysarthria and chorea
175/F/21	NA	154	Penicillamine (2)	Anarthria, severe dystonia and incoordination, nonambulatory
181/M/38	654	381	None	Severe dysarthria, dystonia, tremor, incoordination, nonambulatory
183/M/30	414	607	None	Tremor, incoordination
194/M/11	403	122	None	Mild dystonia and incoordination
200/M/28	809	626	None	Mild dysarthria, incoordination, tremor
203/M/30	689	220	Zinc acetate (3)	Mild dysarthria, incoordination, tremor
205/M/28	397	319	None	Mild dysarthria, dystonia, incoordination
206/F/27	1077	115	Zinc acetate (2)	Severe dysarthria, mild dystonia, incoordination
208/M/21	441	NA	Penicillamine (3)	Anarthria, severe dystonia, incoordination, nonambulatory
209/F/27	285	NA	Zinc acetate (4)	Severe dysarthria, dystonia, tremor, incoordination, nonambulatory
210/M/23	326	310	None	Dysarthria, mild dystonia, incoordination
211/F/28	989	260	None	Mild dysarthria and dystonia
212/M/36	609	234	None	Mild dysarthria, dystonia, tremor, incoordination, psychiatric problems
214/M/31	670	213	Penicillamine (3)	Mild dysarthria, dystonia, tremor
216/F/35	511	251	None	Severe dysarthria, dystonia, tremor, incoordination
218/M/25	856	302	None	Mild dysarthria and tremor
222/F/43	NA	175	None	Dysarthria, dystonia, tremor, incoordination
223/M/24	319	340	Penicillamine (1)	Mild dysarthria, dystonia, severe tremor, incoordination
227/F/37	766	128	None	Dysarthria, dystonia, tremor, incoordination

Abbreviation: NA, not available.
*Incoordination in all patients was related to bradykinesia.

tients, for a total of 55. In addition, we summarize the efficacy and toxicity data in the entire cohort of 55 patients.

METHODS

The patients were diagnosed as having Wilson disease by means of standard criteria previously extensively published.[9-14] Some of the presenting symptoms and diagnostic data gathered at the time of first admission in the 22 new patients described herein are shown in **Table 1**. In addition to the underlying diagnosis of Wilson disease, all patients were diagnosed as having symptoms of a movement disorder attributable to Wilson disease. The institutional review board of the University of Michigan Medical School, Ann Arbor, reviewed and approved the project.

Each patient was admitted for up to 8 weeks in the General Clinical Research Center of the University of Michigan Hospital, Ann Arbor. After initial studies to confirm the diagnosis, obtain informed consent, and establish baseline neurologic and speech function, therapy with tetrathiomolybdate was initiated. In many patients the drug was started at 120 mg/d, with 20 mg between meals 3 times daily and 20 mg with meals 3 times daily. If the patient strongly desired a bedtime snack, a fourth 20-mg dose was given with the snack, for a total initial dose of 140 mg/d. In most patients the between-meals doses were then rapidly escalated during a several-day period, usually to a total dose of about 200 to 260 mg/d. In some patients, the dose was not escalated. The tetrathiomolybdate treatment used in the 22 new patients is given in **Table 2**. In addition to initial dose, Table 2 gives maximum and average dose data. Patients also started zinc therapy early in their 8-week stay, usually 50 mg 3 times per day. Patients did not receive additional tetrathiomolybdate after the initial 8 weeks of therapy.

Two types of toxic effects from tetrathiomolybdate have been encountered. One is an overtreatment anemia, often accompanied by leukopenia, and occasionally by thrombocytopenia. The other is a mild further elevation of aminotransferase enzymes, due to unknown mechanisms. When either was encountered, the patient's tetrathiomolybdate dose was decreased and often the patient was given a drug holiday.

During the 8-week admission, a quantitative neurologic test and a quantitative speech examination were carried out at roughly weekly intervals, by previously published methods,[2-4] standardized for, and extensively evaluated in, Wilson disease. The neurologist (P.H., M.C., and J.K.F.) and speech (K.J.K.) evaluators were not blinded during this open-label study. The main purpose of these weekly tests was to detect neurologic deterioration during initial treatment. An increase of 5 points (scale, 0-38) on the quantitative neurologic examination, or an increase of 3 points (scale, 0-7) on the speech examination, is taken as evidence of significant neurologic deterioration. The patients were discharged on a regimen of zinc maintenance therapy, then returned for an annual visit. The neurologic and speech tests were repeated on an annual basis. The main purpose of these annual examinations was to evaluate the extent of neurologic recovery, if any.

During the 8-week period, assays of "safety variables" were carried out to detect adverse effects of tetrathiomolybdate therapy. These include complete blood cell counts, liver function tests, and amylase, lipase, creatinine, serum urea nitrogen, uric acid, urine protein, and iron variables, all carried out by standard technique in use at the University of Michigan Health System hematologic and biochemistry laboratories.

RESULTS

Table 3 shows the results of the weekly quantitative neurologic testing. Patient 211 showed a 6-point deterioration in week 2, so we scored her as showing deterioration, although her scores varied quite widely during the next 3 weeks. None of the other patients showed a 5-point deterioration (increase) in score. The data demonstrated the minor fluctuations in symptoms from one time to another that are attributable to the level of stress, anxi-

Table 2. Data on Tetrathiomolybdate Dosage, Complications, and Dosage Interventions*

Patient No.	Dosage, mg/d			Complications	Interventions
	Starting	Maximum	Average		
169	140	140	120	. . .	. . .
172	120	320	300	. . .	. . .
173	120	140	120	Mild anemia, leukopenia	None
175	120	200	180	Anemia, leukopenia, thrombocytopenia, and aminotransferase elevations	Drug holiday
181	120	260	180	. . .	. . .
183	140	260	240	. . .	. . .
194	120	200	140	. . .	. . .
200	140	260	260	. . .	. . .
203	140	200	200	. . .	. . .
205	200	200	180	Mild anemia, leukopenia	Drug holiday, then dosage reduction to 60 mg/d
206	140	200	140	Aminotransferase elevations	Drug holiday, then dosage reduction to 60 mg/d
208	120	200	100	Aminotransferase elevations	Dosage reduction to 80 mg/d
209	120	200	120	Mild anemia, leukopenia, thrombocytopenia	Drug holiday, then dosage reduction to 80 mg/d
210	140	140	140	. . .	. . .
211	140	140	140	. . .	. . .
212	140	200	200	. . .	. . .
214	140	200	200	. . .	. . .
216	140	200	120	Mild anemia, leukopenia	Drug holiday, then dosage reduction to 80 mg/d
218	120	120	120	. . .	. . .
222	120	120	120	. . .	. . .
223	120	120	120	. . .	. . .
227	120	140	120	. . .	. . .

*Ellipses indicate none.

ety, fatigue, etc, that can impact on the expression of these signs and symptoms.

Table 4 shows similar data for the speech quantitative testing. No patient showed a 3-point deterioration (increase) in score. Again, the data showed the minor fluctuations in dysarthria from one time to another that are attributable to the psychological and physical status of the patient on the day of testing, as discussed in the preceding paragraph.

Table 5 shows the results of repeat quantitative neurologic testing on annual return visits of the 19 patients who returned, compared with the baseline, which is the first recorded score during the initial 8-week admission. One patient died of variceal bleeding before return, and 2 dropped out. Only 1 patient (patient 210) showed significant (≥5 points) deterioration, in this case between baseline and year 1, and this was clearly related to noncompliance with zinc therapy. Almost all of the patients showed some improvement in scores, generally with most of the improvement between baseline and year 1. This is perhaps best demonstrated by the improvement in mean scores at the bottom of Table 5, which shows that average improvement was predominant in that period and was statistically significant.

Table 6 shows the results of repeat quantitative speech testing on annual return visits of the 19 patients who returned, compared with the baseline, which is the first recorded score during the initial 8-week admission. No patient showed significant (≥3 points) deterioration in score. Many patients showed some improvement in their score over baseline, with most of that improvement occurring between baseline and year 1. This is demonstrated by the mean scores at the bottom of Table 6, which show statistically significant improvement between baseline and year 1. However, unlike the neurologic data, the means for each year in Table 6 suggest that, in some patients, improvement in speech may continue as long as year 3, and indeed, the means of years 2 and 3 are very close to being significantly different.

We saw 2 adverse effects from tetrathiomolybdate therapy in this study (Table 2). Five patients (patients 173, 175, 205, 209, and 216) exhibited bone marrow suppression (**Table 7**), which is attributable to overtreatment and bone marrow depletion of copper. Bone marrow suppression began between weeks 3 and 6 in the 5 patients. Three patients (patients 175, 206, and 208) exhibited elevations of serum aminotransferase enzymes (**Table 8**), due to unknown mechanisms. Enzyme elevations began at the beginning of week 4 in the 3 patients. Mild alkaline phosphatase elevations are expected, because of the initiation of zinc therapy. This is a harmless result of increased induction of the enzyme in the liver by zinc.[15] Both the bone marrow suppression and the aminotransferase elevations were responsive to a drug holiday and/or a reduction in tetrathiomolybdate dose (Table 2).

No patient showed abnormalities of serum urea nitrogen, creatinine, uric acid, and urine protein levels during the 8 weeks of tetrathiomolybdate therapy (data not shown).

COMMENT

In terms of efficacy, the major issue is to avoid the initial neurologic deterioration that occurs about 50% of the time with penicillamine therapy and results in about 25% of patients having permanent, additional, drug-induced

Table 3. Weekly Quantitative Neurologic Scores During the 8 Weeks of Initial Tetrathiomolybdate Therapy*

	Weeks of Therapy								
Patient No.	0	1	2	3	4	5	6	7	8
169	. . .	18.5	. . .	. . .	16	16	. . .	. . .	14.5
172	. . .	5	4.5	. . .	. . .	2	. . .	. . .	3
173	1.5	. . .	. . .	1.5	. . .	. . .	. . .	1	1.5
175	28	. . .	. . .	25	23	24	. . .	26	. . .
181	22	14.5	15.5	20	20	20	18	. . .	. . .
183	. . .	. . .	3.5	3.5	4	. . .	. . .	. . .	2.5
194	6	6.5	7.5	6.5	. . .	5	4.5	4	. . .
200	4	6.5	5.5	4	2.5	. . .	5	6	. . .
203	8.5	8	10	8.5	8.5	. . .	7.5	. . .	. . .
205	4.5	3	. . .	. . .	. . .	2.5	2	2	. . .
206	8.5	9	7	. . .	8	5.5	6	. . .	. . .
208	23	23.5	23	22.5	23	26	25	26	. . .
209	22	19.5	19	23	21.5	22.5	. . .	. . .	. . .
210	3.5	3.5	. . .	3.5	3.5	4	4	. . .	. . .
211	5.5	6	11.5	5.5	. . .	10	. . .	. . .	. . .
212	. . .	. . .	6	4	4	2	. . .	. . .	. . .
214	3	2.5	2	2	. . .	. . .	. . .	. . .	. . .
216	19	19	. . .	21.5	. . .	. . .	. . .	23	21.5
218	7	. . .	4.5	1.5	. . .	1.5	2.5	. . .	3.5
222	9	8.5	7.5	6	7.5	6	5.5	. . .	. . .
223	9.5	5	5	. . .	10	8	8	9.5	. . .
227	8.5	8.5	11	. . .	11	10	6.5	. . .	. . .
Mean	10.7	9.8	8.9	9.2	11.7	10.3	7.9	11.1	7.8
SD	7.9	6.4	5.7	8.3	7.6	8.3	6.5	10.2	7.5
No. of patients	18	17	16	15	16	16	12	9	6

*Score range is 0 (normal) to 38. Ellipses indicate not measured.

Table 4. Weekly Quantitative Speech Scores During the 8 Weeks of Initial Tetrathiomolybdate Therapy*

	Weeks of Therapy								
Patient No.	0	1	2	3	4	5	6	7	8
169	4.5	. . .	4.5	4.5	4.5	. . .	6	4.5	4.5
172	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
173	3	2	2	2	2	2	2	2	. . .
175	6	5.5	5.5	. . .	5.5	5.5	. . .	6	6
181	4.5	4.5	5.5	5.5	7	5.5	7	7	. . .
183	2	1	1	1	1	1	1	. . .	. . .
194	3.5	3.5	3.5	3.5	3.5	. . .	3.5	3.5	3.5
200	3.5	2.5	3.5	2	2	2	2	1.5	. . .
203	3	3	3	3	3	3	. . .	. . .	. . .
205	3	3	. . .	. . .	3	3	3	. . .	. . .
206	5	5	5	5	5	6	5	5	. . .
208	5.5	5	5	5	5	5	5	5	5
209	5	5	6	5.5	5	5.5	5.5	. . .	. . .
210	4.5	4.5	4.5	4.5	4.5	4.5	. . .	. . .	. . .
211	4.5	4.5	4.5	5	4.5	4.5	5	. . .	. . .
212	2	2	2	2	2	1.5	. . .	. . .	. . .
214	3	2	2	2	2	2	. . .	. . .	. . .
216	6	7	7	7	7	7	7	. . .	. . .
218	1	1	1	1	1	1	. . .	1	1
222	3	3	3	3	3	3	3	3	. . .
223	2.5	2.5	2.5	2.5	2.5	. . .	2.5	2.5	. . .
227	3	3	. . .	3	3	3	3	3	. . .
Mean	3.7	3.5	3.7	3.5	3.6	3.6	4.0	3.7	3.9
SD	1.3	1.5	1.6	1.6	1.7	1.8	1.8	1.7	1.6
No. of patients	22	21	20	20	22	19	16	13	6

*Score range is 0 (normal) to 7. Ellipses indicate not measured.

Table 5. Yearly Quantitative Neurologic Scores After Initial Tetrathiomolybdate and Maintenance Zinc Acetate Therapy

		Year*		
Patient No.	Baseline	1	2	3
169	18.5	19.0	18.5	15.5
172	5.0	2.5	2.0	0.5
173	1.5	0.0	1.0	4.0
175		Dropped out		
181	22.0	5.0	7.0	9.5
183	3.5	5.0	2.0	1.0
194	6.0	0.0	3.0	1.0
200	4.0	1.0	1.0	. . .
203	8.5	4.0	2.0	4.0
205		Deceased		
206	8.5	5.5	11.0	9.5
208	23.0	21.0	17.0	16.5
209		Dropped out		
210	3.5	12.0	6.0	3.5
211	5.5	1.0	1.5	2.0
212	6.0	2.0	2.5	0.5
214	3.0	1.0	0.0	0.0
216	19.0	6.0	4.0	3.5
218	7.0	3.0	. . .	1.5
222	9.0	1.5	1.0	0.5
223	9.5	1.0	. . .	. . .
227	8.5	2.0	. . .	. . .
Mean	9.0†	4.9†	5.0	4.6
SD	6.4	5.9	5.5	5.2
No. of patients	19	19	16	16

*Ellipses indicate not measured.
†A paired *t* test comparing baseline vs year 1 is significantly different at $P<.002$.

Table 6. Yearly Quantitative Speech Scores After Initial Tetrathiomolybdate and Maintenance Zinc Acetate Therapy

		Year*		
Patient No.	Baseline	1	2	3
169	4.5	5.0	4.0	4.0
172	3.5	2.5	1.5	1.0
173	3	1.5	2.0	3.0
175		Dropped out		
181	4.5	3.0	2.0	1.0
183	2.0	1.0	0.0	0.0
194	3.5	3.5	3.0	2.0
200	3.5	1.0	0.5	. . .
203	3.0	. . .	2.5	2.5
205		Deceased		
206	5.0	5.0	5.5	5.5
208	5.0	5.0	5.0	5.0
209		Dropped out		
210	4.5	5.5	4.5	. . .
211	4.5	3.0	2.0	1.5
212	2.0	1.0	0.5	0.0
214	3.0	1.0	. . .	0.5
216	6.0	4.0	4.0	3.0
218	1.0	. . .	1.0	1.0
222	3.0	2.5	. . .	1.5
223	2.5	1	. . .	0.5
227	3.0	1.5	. . .	. . .
Mean	3.5†	2.8†	2.5‡	2.0‡
SD	1.2	1.6	1.7	1.6
No. of patients	19	17	15	16

*Ellipses indicate not measured.
†A paired *t* test comparing baseline vs year 1 is significantly different at $P<.001$.
‡A paired *t* test comparing year 2 vs year 3, on the 11 patients in whom both samples were obtained, gives $P = .055$.

damage.[1] In these 22 patients, only 1 was classified as neurologically worsening during the initial 8 weeks of therapy (Table 3), and none was classified as having deterioration in speech (Table 4). Putting these data together with data from the earlier 33 patients described,[4] of whom 1 deteriorated, we have seen a total of 2 neurologic deteriorations in 55 patients treated, for a rate of 3.6%. We speculate that an occasional patient will exhibit continued neurologic deterioration irrespective of the anticopper drug used, whereas penicillamine catalyzes a "drug-induced" deterioration. Our working hypothesis on why the latter happens is that penicillamine aggressively mobilizes copper from the liver, increasing blood copper levels and, in the process, further elevating brain copper levels for a time.

The low rate of neurologic deterioration when tetrathiomolybdate is used for initial therapy is a very positive result, because it allows subsequent recovery starting at a much higher baseline than if the patient deteriorates. During the ensuing period of maintenance therapy, for which we use zinc, substantial improvement occurs (Tables 5 and 6), probably through recovery of neurons that were damaged but not killed by the copper-induced inflammatory process. Most of the improvement occurs during the first year, although with speech, improvement may occur during a longer period (Table 6).

The neurologic and speech recovery data over time in the present study are compared with the original study[4] in **Table 9**. These data show the consistency between the 2 studies in terms of mean baseline values, occurrence of most of the improvement during year 1, and the degree of average improvement.

Alternatives to tetrathiomolybdate for initial therapy, besides penicillamine, include zinc, which appears to be favored by Hoogenraad et al.[16] However, we view zinc as rather slow acting for acutely ill patients, taking perhaps 4 to 6 months to control copper toxicity, during which time the disease may progress. Another alternative is trientine. Although its mechanism is similar to that of penicillamine, it is a more gently acting drug and may not share penicillamine's propensity to make the disease worse initially. We are currently in the midst of a double-blind clinical trial comparing tetrathiomolybdate and trientine for initial use in patients with a neurologic presentation.

A formal toxicity study of tetrathiomolybdate had not been done before these studies, although one is now under way. Approval by the US Food and Drug Administration for this clinical trial was based on extensive animal studies of tetrathiomolybdate during several decades, in which the only toxic effects found were due to copper deficiency.

Adverse effects from tetrathiomolybdate in these studies have been limited to mild bone marrow suppression producing anemia, leukopenia, and occasionally thrombocytopenia, and to mild elevations of aminotrans-

Table 7. Blood Count Studies During the 8 Weeks of Initial Tetrathiomolybdate Therapy

	Weeks of Therapy								
	0	1	2	3	4	5	6	7	8
Mean Blood Counts in the 17 Patients Who Were Stable									
HGB, g/dL	13.2	13.1	13.0	13.2	13.3	13.2	12.9	12.4	13.0
WBCs/μL	4300	4800	4200	6200	4200	4000	4400	4100	3900
Platelets, $\times 10^3$/μL	121	117	117	133	119	124	135	132	134
No. of patients	17	17	17	17	16	16	12	11	5
Mean Blood Counts in the 5 Patients Who Showed Bone Marrow Suppression									
HGB, g/dL	13.8	12.2	12.0	11.5	11.0	10.5	9.8	10.8	10.3
WBCs/μL	5800	4200	4500	4000	3700	5800	3500	4400	4600
Platelets, $\times 10^3$/μL	112	90	102	104	98	90	86	122	130
No. of patients	5	5	5	5	5	4	4	3	2

Abbreviations: HGB, hemoglobin; WBCs, white blood cells.

Table 8. Liver Function Studies During the 8 Weeks of Initial Tetrathiomolybdate Therapy

	Weeks of Therapy								
	0	1	2	3	4	5	6	7	8
Mean Liver Function Values in the 19 Patients Who Were Stable									
Bilirubin, mg/dL	0.9	0.6	0.6	0.6	0.7	0.7	0.7	0.6	0.6
Albumin, g/dL	3.6	3.4	3.4	3.5	3.5	3.5	3.5	3.4	3.5
ALT, IU/L	36	36	37	37	34	56	63	54	74
AST, IU/L	38	34	32	31	32	32	41	36	44
LDH, IU/L	168	170	163	161	161	194	204	166	157
Alk phos, U/L	93	94	99	102	103	118	116	111	122
No. of patients	19	18	18	19	17	17	13	11	6
Mean Liver Function Values in the 3 Patients Who Showed Aminotransferase and Alk Phos Elevations									
Bilirubin, mg/dL	0.9	0.9	0.6	0.6	0.8	0.8	0.9	0.4	0.4
Albumin, g/dL	3.7	3.5	3.4	3.3	3.2	3.1	3.4	3.3	3.2
ALT, IU/L	81	84	82	288	378	413	354	174	89
AST, IU/L	67	84	53	125	148	139	148	50	36
LDH, IU/L	251	301	221	210	198	188	251	190	164
Alk phos, U/L	137	133	137	170	212	225	271	469	489
No. of patients	3	3	3	3	3	3	2	1	1

Abbreviations: Alk phos, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase.
SI conversion factor: To convert bilirubin to micromoles per liter, multiply by 17.1.

ferase enzymes. The bone marrow effects appear to be due to depletion of copper and are responsive to a drug holiday or dose reduction. The frequency of anemia or leukopenia was much higher in the current study (5 of 22 patients) than in the original study (1 of 33 patients). One difference is that the number of patients receiving a daily dose of 200 mg or more was only 15 of 33 in the original study and was 14 of 22 in the present study. A second difference is that the dose escalation was considerably more rapid in the current study, usually taking less than a week, while it occurred during 2 to 3 weeks in the original study. Probably the most important difference is that in the original study, escalation was based on the presence of free copper in the blood. This was copper unaccounted for by ceruloplasmin or tetrathiomolybdate binding. In the current study, escalation was more arbitrary, aimed at quelling copper toxicity quickly, since we had seen so little problem with higher doses in the original study.

The other adverse effect, aminotransferase elevations in 3 of 22 patients, was not detected at all in our original study of 33 patients. We are not sure what causes aminotransferase elevations, but we speculate that tetrathiomolybdate is removing copper from various hepatic pools, including metallothionein, and that this causes some additional hepatitis. Since we have not seen this adverse effect from tetrathiomolybdate use in a variety of other clinical uses such as for cancer[17] and macular degeneration, where it is used for antiangiogenic purposes, nor in a variety of animal studies, we suspect it occurs only in the face of high hepatic copper loading. Again, we suspect that the reason we saw aminotransferase elevations here but not in the original 33 patients relates to the more rapid and arbitrary tetrathiomolybdate dose escalation.

Both of these adverse effects are quickly responsive to a drug holiday and/or dose reduction. Both clearly are related to dose. For example, in the present study, 7 of the 8 adverse effects occurred in the 14 patients receiving 200 mg or more of tetrathiomolybdate per day (Table 2), whereas only 1 occurred in the 8 patients who received 140 or 120 mg. Since our data indicate no effi-

Table 9. Neurology and Speech Scores Over Time in the 2 Studies

	Baseline	Year 1	Year 2	Year 3
Neurology Scores				
Original study[4]				
Mean	8.1	4.8	2.5	3.5
SD	6.1	6.2	4.8	3.9
No. of patients	26	17	10	11
Present study				
Mean	9.0	4.9	5.0	4.6
SD	6.4	5.9	5.5	5.2
No. of patients	19	19	16	16
Speech Scores				
Original study				
Mean	3.3	2.1	1.8	1.8
SD	1.7	1.6	1.3	1.7
No. of patients	24	22	15	15
Present study				
Mean	3.5	2.8	2.5	2.0
SD	1.2	1.6	1.7	1.6
No. of patients	19	17	15	16

cacy advantage of higher doses, we now recommend daily doses no higher than 120 mg/d for the initial treatment of Wilson disease, to minimize adverse effects.

In summary, tetrathiomolybdate shows excellent efficacy for the initial treatment of patients presenting with the movement disorder symptoms of Wilson disease. Only 2 (4%) of 55 patients worsened during the 8 weeks of tetrathiomolybdate therapy, compared with an estimated 50% who are treated initially with penicillamine. This stabilization of the clinical state during the initial period while copper toxicity is controlled then allows very good recovery of much neurologic function during the succeeding year or two.

Two adverse effects predominate. One is overtreatment bone marrow suppression. Since the bone marrow requires copper for cellular proliferation, higher doses of tetrathiomolybdate causing bone marrow depletion of copper result in bone marrow cellular suppression. The other adverse effect is elevation of serum aminotransferase enzymes, possibly due to hepatic mobilization of copper in livers already loaded with copper. Both adverse effects are dose related and occur much less frequently if the daily dose of tetrathiomolybdate does not exceed 120 mg. Since there does not appear to be an efficacy advantage of higher tetrathiomolybdate doses, we recommend 120 mg/d for initial therapy in Wilson disease, to minimize adverse effects. Both adverse effects, if they do occur, are quickly responsive to drug holiday and/or dose reduction.

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REFERENCES

1. 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; 44:490-493.
2. Brewer GJ, Dick RD, Yuzbasiyan-Gurkan V, Tankanow R, Young AB, Kluin KJ. Initial therapy of patients with Wilson's disease with tetrathiomolybdate. *Arch Neurol.* 1991;48:42-47.
3. Brewer GJ, Dick RD, Johnson V, et al. Treatment of Wilson's disease with ammonium tetrathiomolybdate, I: initial therapy in 17 neurologically affected patients. *Arch Neurol.* 1994;51:545-554.
4. Brewer GJ, Johnson V, Dick RD, Kluin KJ, Fink JK, Brunberg JA. Treatment of Wilson disease with ammonium tetrathiomolybdate, II: initial therapy in 33 neurologically affected patients and follow-up with zinc therapy. *Arch Neurol.* 1996; 53:1017-1025.
5. Mills CF, El-Gallad TT, Bremner I. Effects of molybdate, sulfide, and tetrathiomolybdate on copper metabolism in rats. *J Inorg Biochem.* 1981;14:189-207.
6. Bremner I, Mills CF, Young BW. Copper metabolism in rats given di- or trithiomolybdates. *J Inorg Biochem.* 1982;16:109-119.
7. Mills CF, El-Gallad TT, Bremner I, Wenham G. Copper and molybdenum absorption by rats given ammonium tetrathiomolybdate. *J Inorg Biochem.* 1981;14: 163-175.
8. Gooneratne SR, Howell JM, Gawthorne JM. An investigation of the effects of intravenous administration of thiomolybdate on copper metabolism in chronic Cu-poisoned sheep. *Br J Nutr.* 1981;46:469-480.
9. Brewer GJ, Hill GM, Prasad AS, Cossack ZT, Rabbani P. Oral zinc therapy for Wilson's disease. *Ann Intern Med.* 1983;99:314-319.
10. Hill GM, Brewer GJ, Prasad AS, Hydrick CR, Hartmann DE. Treatment of Wilson's disease with zinc, I: oral zinc therapy regimens. *Hepatology.* 1987;7:522-528.
11. Brewer GJ, Hill GM, Dick RD, et al. Treatment of Wilson's disease with zinc, III: prevention of reaccumulation of hepatic copper. *J Lab Clin Med.* 1987;109:526-531.
12. Brewer GJ, Hill G, Prasad A, Dick R. Treatment of Wilson's disease with zinc, IV: efficacy monitoring using urine and plasma copper. *Proc Soc Exp Biol Med.* 1987; 184:446-455.
13. 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; 132:264-278.
14. Brewer GJ. *Wilson's Disease: A Clinician's Guide to Recognition, Diagnosis, and Management.* Boston, Mass: Kluwer Academic Publishers; 2001.
15. 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; 114:520-526.
16. 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; 77:137-146.
17. Brewer GJ, Dick RD, Grover DK, et al. Treatment of metastatic cancer with tetrathiomolybdate, an anticopper, antiangiogenic agent: phase I study. *Clin Cancer Res.* 2000;6:1-10.