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METALS

Randomized Placebo-Controlled Trial of 2,3-Dimercapto-1-propanesulfonate (DMPS) in Therapy of Chronic Arsenicosis Due to Drinking Arsenic-Contaminated Water

Debendra Nath Guha Mazumder,* Binay Krishna De, Amal Santra, Nilima Ghosh, Subhankar Das, Sarbari Lahiri, and Tapas Das

Department of Gastroenterology and Medicine, Institute of Postgraduate Medical Education and Research, Calcutta, India

ABSTRACT

Background: *Chronic arsenic toxicity, producing various clinical manifestations, is currently epidemic in West Bengal, India, Bangladesh, and other regions of the world. 2,3-Dimercapto-1-propanesulfonate, a chelating agent, increases excretion of arsenic in urine to several times the prechelation concentration but the therapeutic efficacy of 2,3-dimercapto-1-propanesulfonate in the management of chronic arsenic toxicity has been incompletely evaluated. We investigated the clinical use of 2,3-dmercapto-1-propanesulfonate in such patients.* ***Methods:*** *Twenty-one consecutive patients with chronic arsenicosis were individually randomized into 2 groups: 11 patients (9 males and 2 females, age 30.63 ± 11.4 years) received 2,3-dimercapto-1-propanesulfonate 100-mg capsules 4 times a day for 1 week and repeated in the 3rd, 5th, and 7th week with no drug during the intervening period. The other 10 patients (5 males and 5 females, age 34.4 ± 14.41 years) were given placebo capsules (resembling 2,3-dimercapto-1-propanesulfonate) in the same schedule. The consumption of arsenic-contaminated water was terminated by all 21 subjects. Initial and posttreatment urinary arsenic excretion was determined in all cases. Sequential excretion of urinary arsenic was determined during the treatment*

* Correspondence: Dr. Debendra Guha Mazumder, 37/C Block B, New Alipore, Calcutta 700053, West Bengal, India. Fax: 91/033-475-1799; E-mail: dngm@apexmail.com

of 2 drug- and 1 placebo-treated cases. The clinical features were evaluated by an objective scoring system before and after treatment. Routine investigation including liver function test and skin biopsy were also done before and after the treatment. Drug-associated toxicity was tabulated. ***Results****: Therapy with 2,3-dimercapto-1-propanesulfonate caused significant improvement in the clinical condition of chronic arsenicosis patients as evidenced by significant reduction of total clinical scores from 8.90 ± 2.84 to 3.27 ± 1.73; $p < 0.0001$. Exposure cessation alone with placebo treatment also reduced clinical scores (8.50 ± 1.96 to 5.40 ± 2.12; $p < 0.003$), but the posttreatment total clinical score of 2,3-dimercapto-1-propanesulfonate-treated patients (3.27 ± 1.73) was significantly lower than that of placebo-treated patients (5.40 ± 2.12; $p < 0.01$). The most significant improvement was noted in regard to the clinical scores of weakness, pigmentation, and lung disease. No difference was noted between groups in the hematological and biochemical parameters (which were normal) and skin histology before and after treatment. No 2,3-dimercapto-1-propanesulfonate-related adverse effects were noted. Total urinary excretion of arsenic in 2,3-dimercapto-1-propanesulfonate-treated cases increased significantly following drug therapy, with no increase in placebo-treated cases.* ***Conclusion****: 2,3-Dimercapto-1-propanesulfonate treatment caused significant improvement in the clinical score of patients suffering from chronic arsenic toxicity. Increased urinary excretion of arsenic during the period of therapy is the possible cause of this improvement.*

BACKGROUND

Chronic arsenic (As) toxicity due to drinking of As-contaminated water has been reported from many countries, but the number of affected people in West Bengal, India, and Bangladesh is unprecedented. It is estimated that about 6 million people are exposed to As-contaminated drinking water (As level > 0.05 mg/L) in 8 districts of West Bengal (1–3). Hyperpigmentation and keratosis of the skin are endemic with weakness, anemia, burning sensation of the eyes, solid edema of the legs, liver fibrosis, chronic lung disease, gangrene of the toes, and neuropathy as further manifestation of chronic arsenicosis (4). Chronic As toxicity is an established cause of skin cancer and recent studies strengthen the evidence that it also causes lung and urinary bladder cancer (5). Despite the magnitude of this potentially fatal toxicity, there is no effective therapy for this condition; patients once affected may not recover even after remediation of the As-contaminated water (6). A cohort of 24 subjects with chronic arsenicosis, followed for 2–10 years after exposure, showed improvement of cutaneous manifestations in only 45% of cases while new symptoms of lung disease appeared in 41.6% of cases (7). There is a compelling need for an effective pharmacotherapeutic agent to reduce the body burden of As, alleviate toxicity, and prevent As-related cancer.

In the 1940s, 2,3-dimercapto-1-propanol, commonly known as British Anti-Lewisite (BAL) (8) was found to be an effective antidote in acute As poisoning. 2,3-Dimercapto-1-propanesulfonate (DMPS) (9) and meso-2,3-dimercaptosuccinic acid (DMSA) (10) are much more soluble in water and can be administered orally. Evaluations of arsine and As trioxide in rabbits (11,12), mice (13,14), and guinea pigs (15) all favor treatment with DMSA over BAL. The significantly lower toxicity and the ease of administration contributed to the clinical consensus that DMSA and DMPS, not BAL, are the first choice of therapy for human As poisoning (16). In our earlier controlled human study, DMSA was not found to be more effective than placebo in reversal of the clinical biochemical responses or histological responses to chronic arsenicosis (17).

We report here results of our study of a prospective, randomized, single-blind, placebo-controlled trial to evaluate the efficacy and safety of DMPS in patients with chronic arsenicosis caused by drinking As-contaminated water.

METHODS

Study Design

Between June 1998 and January 2000, we conducted a prospective, randomized, placebo-controlled, single-blind study of previously untreated patients with chronic arsenicosis. Patients received either 100 mg DMPS (Dimaval, Heyl-Vertriebs-GmbH, Germany) 4 times per day

orally or matching placebo for 1 week, repeated in the 3rd, 5th, and 7th week with no medication during the intervening period. Both case and control patients were provided with a standard hospital diet, safe water (As < 10 μg/L), and similar symptomatic treatment. For the treatment of bronchitis, identical courses of antibiotics were given for 1 week. The same bronchodilator was used for the treatment of dyspnea caused by bronchospasm.

The design of this study was otherwise similar to that of the DMSA study (17) with a few modifications. Briefly, all the patients included in the study were selected from the As clinic on the basis of a history of drinking As-contaminated water (As content > 50 μg/L) for more than 3 years associated with clinical features of chronic As toxicity. A large number of cases attended the As clinic; the selected subjects were a consecutive convenience sample of individuals who consented to hospitalization for the total period of study and fulfilled the inclusion criteria. Randomization occurred after admission. No two members of the same family were included.

Patients were evaluated by an objective scoring system before and after treatment. The scoring system followed was similar to that of the DMSA study trial. Although many symptomatic parameters recorded were subjective, the objective parameters included pigmentation, keratosis, chest signs (rales and rhonchi), hepatomegaly, and splenomegaly. Flushing of the face, edema of the legs/hands, ascites, and loss of ankle jerk were also included in the scoring system (Table 1). Breathlessness on accustomed exertion, mild exertion, or at rest were defined as mild (Score 1), moderate (Score 2), or severe (Score 3), respectively. Any possible therapy-related side effect was monitored in every patient. All the patients were hospitalized throughout the study period. The institutional review board approved the study and all patients gave written informed consent.

Patients

To be eligible, patients had to be at least 18 years of age and have clinical evidence of chronic As toxicity (all had spotty pigmentation and keratosis), with a history of drinking As-contaminated water (As content > 50 μg/L) for more than 3 years.

Table 1

System of Clinical Scoring of the Symptoms and Signs Before and After Treatment with DMPS and Placebo

Symptoms and Signs	None	Mild	Moderate	Severe
Weakness	0	1		
Cough	0	1		
Dyspnea	0	1	2	3
Rales, Rhonchi	0	1		
Hepatomegaly	0	1 (14 cm span)	2 (16 cm)	3 (>16 cm)
Splenomegaly	0	1 (2 cm)	2 (4 cm)	3 (>4 cm)
Pigmentation	0	1 (diffuse)	2 (spotty)	3 (blotchy)
Keratosis	0	1 (thickening)	2 (few modules)	3 (multiple nodules)
Flushing of face	0	1		
Conjunctivitis nonpitting	0	1		
Edema leg/hand	0	1		
Abdominal pain	0	1		
Anorexia	0	1		
Nausea	0	1		
Diarrhea	0	1		
Hearing defect	0	1		
Claudication	0	1		
Hand/leg ulcers	0	1		
Paresthesia	0	1 (only legs)	2 (leg + hands)	
Pallor	0	1		
Ascites	0	1		
Loss of ankle jerk	0	1		

Maximum score: 33.

Patients were excluded for any of the following reasons: termination of As-contaminated drinking water for more than 3 months before; treatment with other chelating agents; a history of smoking, addiction to alcohol, taking hepatotoxic drugs; and serum positive for hepatitis B virus surface antigen. Women who were pregnant or breastfeeding were also excluded.

Investigations

Before entry into the study, each participant underwent evaluation of routine hemogram, urine and stool analysis, blood biochemistry, liver function tests, prothrombin time, and screening for hepatitis B surface antigen. Abdominal ultrasonography and upper gastrointestinal endoscopy were employed to evaluate portal hypertension.

Skin biopsies were taken from unexposed areas by punch biopsy technique for histologic evaluation before and after treatment on 4 patients of the DMPS group and 3 patients of the placebo group. Hyperkeratosis, acanthosis, papillomatosis, and parakeratosis, the characteristic features of chronic As toxicity, were evaluated objectively before and after therapy by measuring with an ocular micrometer as described in the DMSA study (17) by a pathologist unaware of the treatment category.

Measurement of As in Urine and Water

Urine samples were collected for 2 consecutive days before and at 24 hours after initiating the drug or placebo. Aliquots of the 24-hour urine samples were immediately deep-frozen and preserved until analyzed by atomic absorption spectroscopy using a method based on that of Atallah and Kalman (18) following an alkali-induced sample digestion procedure. Briefly, an aliquot of urine (1 mL) was wet digested with 1 mL 20% NaOH and 650 mg potassium persulfate for 5 hours at 90°C. After digestion, each sample was diluted to a volume of 10 mL with highly purified distilled deionized (Millipore quality) water. Digested urine samples were analyzed by hydride generation atomic absorption (HGAA) spectroscopy using a Perkin Elmer AA100 atomic absorption spectrophotometer equipped with a flow injection atomic spectroscopy system (FIAS–100) for detecting combined arsine As species (18). The reagents for flow injection analysis and hydride generation were sodium borohydride 0.2% in 0.05% sodium hydroxide used as a reductant and 2% hydrochloric acid used as an acidic carrier solution for the hydride generation. Nitrogen was used as the carrier gas. The detection limit was ascertained and accuracy maintained by analysis of a sample from NIST (formerly the National Bureau of Standards), Washington, DC, and in-house-prepared spiked urine samples. The As concentrations of pretreatment and 24-hour posttreatment urine samples of all DMPS and placebo-treated cases were determined.

The urine As of 2 drug-treated and 1 placebo-treated subjects was analyzed in the progressive weeks of drug/placebo treatment as well as during the off weeks.

The As content of water samples consumed by the patients was analyzed by HGAA following flow injection analysis as above (18).

Statistical Analysis

The significance of the differences between parametric data obtained in the DMPS and placebo groups was calculated by Student's *t*-test. The clinical scores of the patients before and after therapy were compared by one-way analysis of variance (ANOVA). For nonparametric data, Chi-square with Yates' correction, as applicable, was used.

RESULTS

Twenty-one patients were enrolled in the study. Ten were randomly assigned to the placebo group and 11 to the DMPS group. Demographic variables, degree of As exposure, total clinical score, and results of baseline investigations of patients in each group are summarized in Table 2. There were no significant differences in age, duration of As exposure and its concentration in drinking water, pre-therapy urinary As level, objective scores of clinical features, and baseline investigation data between patients of these 2 groups.

Therapy with DMPS caused significant improvement in clinical condition of chronic arsenicosis patients as evidenced by significant reduction of the total clinical score from 8.90 ± 2.84 to 3.27 ± 1.73; $p < 0.0001$. The placebo-treated cases also improved (8.50 ± 1.96 to 5.40 ± 2.12; $p < 0.003$) (Fig. 1), but the posttreatment total clinical score of DMPS-treated patients (3.27 ± 1.73) was significantly lower than that of placebo-treated patients (5.40 ± 2.12; $p < 0.01$). The clinical score improvement of DMPS-treated patients was mostly in the categories in regard to weakness, pigmentation, and lung disease (Table 3). There was no statistically significant difference of any of the symptom scores in regard to pre- and posttreatment values in placebo-treated cases (Table 4). The improved clinical score of the placebo-treated cases was thought to relate to an adequate hospital diet, rest, and cessation of exposure.

Table 2

Baseline Characteristics of the Patients

	DMPS (N = 11)	Placebo (N = 10)	p Value
Demographic Variables			
Age (years)	30.63 ± 11.40	34.4 ± 14.41	0.525
Sex (M:F)	9:2	5:5	
Degree of As Exposure			
As (mg/L) in drinking water	0.64 ± 0.49	0.98 ± 1.02	0.35
Duration of As exposure (years)	21.45 ± 11.57	17.00 ± 4.78	0.27
Urinary As (μg/L)	44.05 ± 21.10	48.72 ± 21.20	0.708
Total Clinical Score	8.90 ± 2.84	8.50 ± 1.96	0.708
Hemogram			
Hemoglobin (g/dL)	10.80 ± 1.66	11.29 ± 1.47	0.51
Total leucocytes (mm^3)	7800 ± 1329	7800 ± 713	1.00
Neutrophils (%)	62.45 ± 8.32	65.14 ± 8.33	0.51
Lymphocytes (%)	27.90 ± 8.32	29.42 ± 8.01	0.69
Blood Biochemistry			
Sugar (mg/dL)	80.45 ± 20.32	79.71 ± 11.88	0.29
Urea (mg/dL)	21.90 ± 8.46	22.25 ± 5.17	0.56
Albumin (g/dL)	4.33 ± 0.40	4.04 ± 0.67	0.326
Globulin (g/dL)	3.51 ± 0.70	3.37 ± 0.39	0.579
ALT (IU/L)	41.50 ± 21.43	25.85 ± 16.07	0.106
AST (IU/L)	42.80 ± 2.84	38.33 ± 14.22	0.637
ALP (IU/L)	182.45 ± 67.33	155.57 ± 67.45	0.23

No significant difference in hematological values or blood biochemistry was observed among subjects treated with either DMPS or placebo, before or after treatment (Table 5). No adverse symptom or any abnormal hematological or biochemical alteration was noted among DMPS- or placebo-treated cases.

DMPS treatment caused a significant increase of the 24-hour urinary As excretion posttreatment (110.32 ± 64.79 μg/L) compared to pretreatment (44.05 ± 21.10 μg/L, $p < 0.05$). No significant difference in urinary As excretion was observed between pre- (48.72 ± 21.20 μg/L) and post- (40.57 ± 15.09 μg/L) urine As of the placebo group.

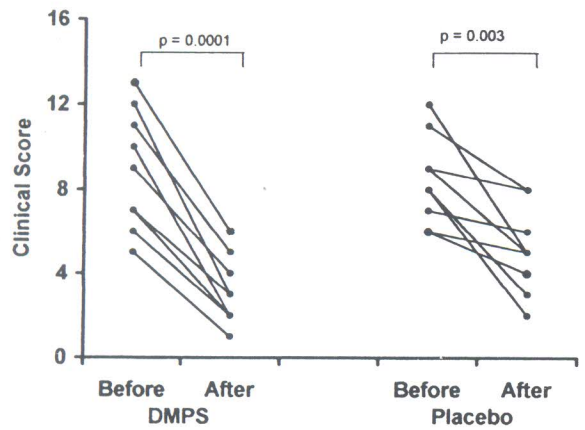

Figure 1. Clinical score of patients before and after therapy with DMPS and placebo.

Serial measurements of 24-hour urine As of 2 DMPS-treated cases showed the highest values within 24 hours of its administration. The concentrations reached baseline after remaining high throughout the first week of therapy. In the subsequent weeks, the urine As remained near the baseline during the drug-free period with some increase during the subsequent courses of DMPS therapy (Figure 2). Urinary As did not show any significant fluctuation during the three courses of placebo therapy (Figure 3).

The histological abnormalities of the skin biopsy tissues of both DMPS- and placebo-treated cases were unaffected by therapy.

DISCUSSION

This is the first randomized, placebo-controlled, single-blind trial with DMPS, a chelating agent, showing significant clinical improvement in patients suffering

Table 3

Pre- and Posttreatment Individual Scores of Patients Treated with DMPS (Case) and Placebo (Control)

	Pigmentation		Keratosis		Weakness		Hepatomegaly		Neuropathy		Lung Disease	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Case												
1	2	1	3	2	1	0	0	0	0	0	0	0
2	2	1	2	2	1	0	1	1	1	0	3	2
3	2	1	2	0	0	0	1	0	0	0	0	0
4	1	1	1	1	1	0	1	0	0	0	3	0
5	1	1	1	1	1	0	1	0	0	0	1	0
6	2	2	1	1	1	0	1	1	1	0	3	0
7	1	1	1	1	1	0	0	0	0	0	2	0
8	1	0	1	0	1	0	1	1	0	0	2	2
9	2	1	2	1	1	0	1	0	0	0	3	0
10	1	1	2	2	1	0	1	1	1	1	3	0
11	1	0	1	1	1	0	1	1	0	0	0	0
Control												
1	2	1	2	1	1	0	1	1	0	0	3	2
2	1	1	1	1	1	0	0	0	0	0	1	1
3	1	1	1	1	1	1	0	0	0	0	3	2
4	1	1	1	1	0	0	1	1	1	1	2	2
5	3	2	3	2	0	0	0	0	0	0	1	0
6	3	3	3	3	1	0	1	1	1	1	1	2
7	1	1	1	1	1	0	1	1	0	0	0	0
8	1	1	1	1	1	1	1	1	0	1	0	1
9	1	0	0	0	1	1	0	0	2	0	4	1
10	2	0	1	0	1	1	2	0	1	1	0	0

Table 4

Clinical Score of Patients Before and After Therapy

Clinical Features	Drugs	Before	After	p Value
Pigmentation	DMPS	1.45 ± 0.52	0.90 ± 0.54	0.02
	Placebo	1.60 ± 0.84	1.10 ± 0.87	0.20
Keratosis	DMPS	1.54 ± 0.68	1.09 ± 0.70	0.14
	Placebo	1.40 ± 0.96	1.11 ± 0.87	0.47
Weakness	DMPS	0.91 ± 0.30	0.00 ± 0.00	0.00000031
	Placebo	0.80 ± 0.42	0.40 ± 0.52	0.07
Hepatomegaly	DMPS	0.82 ± 0.40	0.45 ± 0.52	0.08
	Placebo	0.70 ± 0.67	0.50 ± 0.53	0.46
Neuropathy	DMPS	0.27 ± 0.46	0.09 ± 0.30	0.29
	Placebo	0.50 ± 0.70	0.40 ± 0.51	0.72
Lung disease	DMPS	1.82 ± 1.33	0.36 ± 0.80	0.005
	Placebo	1.50 ± 1.43	1.10 ± 0.87	0.46
Total scoring	DMPS	8.90 ± 2.84	3.27 ± 1.73	0.00017
	Placebo	8.50 ± 1.96	5.40 ± 2.12	0.003

Table 5

Hemogram and Blood Biochemistry of the Patients Before and After Therapy

Clinical Features	Drugs	Before	After	p Value
Hb (g/dL)	DMPS	10.8 ± 1.66	11.09 ± 1.75	0.59
	Placebo	11.29 ± 1.47	11.75 ± 0.91	0.57
Total WBC	DMPS	7800 ± 1329	7918 ± 1551	0.85
(count/mm^3)	Placebo	7800 ± 713	8487 ± 2981	0.56
Neutrophils (%)	DMPS	62.45 ± 8.32	63.36 ± 11.83	0.79
	Placebo	65.14 ± 8.33	60.86 ± 9.99	0.43
Lymphocytes (%)	DMPS	27.90 ± 7.50	28.09 ± 11.27	0.96
	Placebo	29.42 ± 8.01	31.43 ± 10.26	0.68
Urea	DMPS	21.90 ± 8.46	25.18 ± 5.17	0.56
	Placebo	22.25 ± 5.17	21.50 ± 5.37	0.64
Albumin (g/dL)	DMPS	4.34 ± 0.41	4.35 ± 0.61	0.95
	Placebo	4.04 ± 0.68	4.61 ± 0.36	0.07
Globulin (g/dL)	DMPS	3.52 ± 0.71	3.71 ± 1.04	0.46
	Placebo	3.37 ± 0.39	3.17 ± 0.59	0.30
ALT (IU/L)	DMPS	41.5 ± 21.44	32.8 ± 4.41	0.23
	Placebo	25.86 ± 16.07	32.29 ± 15.20	0.45
AST (IU/L)	DMPS	42.8 ± 22.83	31.7 ± 7.02	0.52
	Placebo	38.33 ± 14.22	33.33 ± 7.28	0.43

from chronic As toxicity (compared to placebo treatment) after 4 weeks of drug administration with 3 intervening weeks without medication. There was also clear evidence of increased As excretion in urine following DMPS administration. Although the increases in excretion were less remarkable during subsequent weeks of therapy, there was a definite increase in excretion above baseline concentrations, an increase not seen in the previous study of DMSA (17).

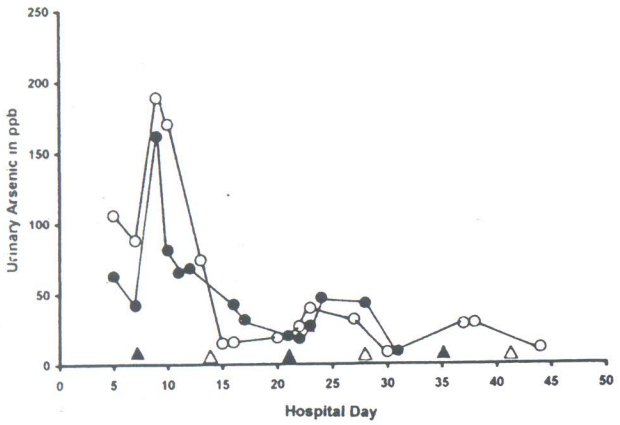

Figure 2. Serial concentrations of 24-hour urine As of 2 patients treated with DMPS showing increased As excretion following drug therapy. Patient 1 (●) and patient 2 (○). ▲ Drug and △ drug withdrawn.

The capacity of chelating agents to improve the clinical outcome in the cases of subacute or chronic As exposure has not been previously investigated in animal experiments or in carefully controlled human clinical trials (19). Case series of patients undergoing dimercaprol treatment for subacute arsenical dermatitis and other complications of syphilis treatment with organic arsenical medication (20) suggested that chelation may accelerate clinical improvement, but these early studies were conducted without rigorous controls and the clinical relevance to long-term ingestion of inorganic As is uncertain.

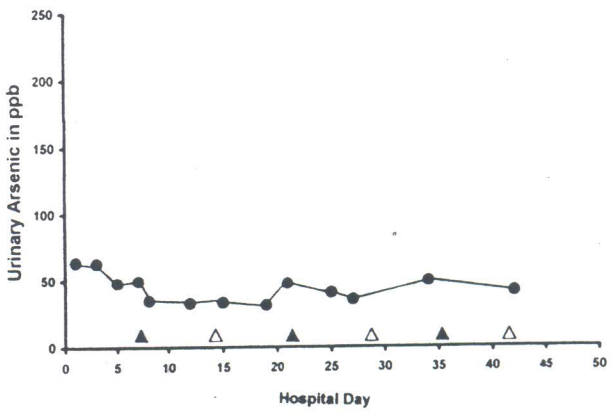

Figure 3. Serial concentrations of 24-hour urine As in a placebo-treated subject. ▲ Placebo and placebo △ withdrawn.

In our earlier placebo-controlled study, we observed that DMSA was globally ineffective in the therapy of chronic As toxicity in man (17).

DMPS appears to be a clinically superior chelating agent than DMSA in the treatment of arsenicosis. The administration of DMPS to fasted normal male volunteers shows DMPS to be excreted in the urine over a longer period of time than DMSA (16). After administration of a single dose of DMPS 300 mg orally in 13 subjects consuming As in drinking water for a prolonged period, urine excretion of As was several-fold that of prechelation levels (21).

DMPS appears to be biotransformed in humans to acyclic and cyclic disulfides whereas DMSA in humans is biotransformed almost completely to a DMSA–CySH (1:2) mixed disulfide (22). A DMPS–cysteine mixed disulfide has been found only in minute amounts after DMPS administration (16). A major difference between DMSA and DMPS is that the latter is distributed both extracellularly and, to a small extent, intracellularly (23–25). Both renal and biliary excretion of DMPS occurs (23).

Chelating agents have been used for more than 50 years in the treatment of metal intoxication (26). DMPS is a chelating agent that belongs to the vicinal dithiol group (27). Because of the 2 neighboring sulfhydryl (SH) groups, DMPS has a high affinity for many heavy metals that have an affinity for sulfur and forms stable complexes with them (27). The 2 SH groups also give rise to its reductive properties (28,29). The polar sulfonic acid group influences primarily the physicochemical behavior and is responsible for water solubility of DMPS (30) and thus for some of its pharmacokinetic properties. DMPS forms stable complexes with many heavy metals (16,31). Complexes with cadmium, cobalt, copper, nickel, mercury, and zinc are water-soluble, while the lead complex is precipitated (32). The majority are chelates, i.e., complexes in which the heavy metals are bound into a ring structure (16). DMPS forms stable complexes with various organic and inorganic As compounds (33–35) predominantly with 1:1 stoichiometry (35).

DMPS is not a new drug. As early as in 1958, the former Soviet Union established it as an official drug. It was subsequently synthesized and marketed as Dimaval by Heyl in Berlin, Germany, and became available to more of the Western world. It has been used mostly for treating humans with mercury (36) and lead (37) intoxication. It is registered in Germany with the BGA (their FDA) for the treatment of mercury poisoning. However, the few reports available to date regarding its efficacy in chronic As toxicity have been inconclusive. Kew et al. (38) found no improvement in peripheral neuropathy of 4 months' duration after 300 mg/d of DMPS for 3 weeks and 1.2 g/d of DMSA for 2 weeks. However, full recovery after treatment with DMPS (without any evidence of prolonged renal or neurological impairment) was observed in 2 cases of acute As toxicity caused by ingestion of large a quantity of As (1 g and 4 g) (39).

Although DMPS showed unequivocal improvement of several clinical symptoms of chronic arsenicosis in the present study, there was no significant improvement of important features like keratosis, neuropathy, or hepatomegaly. There was also no improvement of skin histology in the drug-treated cases. Since the chronic arsenicosis victims treated in this study had been exposed for many years (21.45 $\pm$ 11.57 years), it may be unrealistic to expect reversal by 4 weeks of drug therapy. To assess the long-term efficacy of DMPS on the course of chronic As toxicity (including prevention of development of As-related cancer), a trial of prolonged therapy seems merited. The plan of treatment might be similar to the protocol of prolonged therapy for the management of other metallotoxicity, e.g., hemochromatosis (due to iron overload) or Wilson's disease (due to copper overload) by chelating agents. There were no drug-related side effects nor any hematological and biochemical alteration in any of the 11 cases treated for 4 weeks, and DMPS appears to be a safe drug, but extended observations are needed.

Major limitations of the study include the utilization of single-blind design (because of institutional logistic problems) and the use of some subjective criteria. This might create a major concern about the potential impact of observer bias on the results. However, objective parameters like pigmentation, keratosis, chest signs (rales and rhonchi), and hepatomegaly were also included in the scoring system. In the absence of well-published criteria defining chronic arsenicosis, an arbitrary system of clinical scoring was used to evaluate the efficacy of chelation therapy. The scoring system was not validated before implementation, but limitation of the score to the presence or absence of symptoms like weakness and paresthesia (1 or 0) was intended to improve objectivity. The same clinician evaluated all cases, obviating interevaluator variability, but not observer bias.

The randomization of subjects in the present study to DMPS or placebo appears to have resulted in significant differences with respect to the gender composition of the 2 groups. The DMPS group was predominantly male (82%) compared to an even split in the placebo group. Although one cannot completely rule out the effect of gender difference in the outcome of the results, objective evidence of improvement of pigmentation rules out the possibility of less reporting by Indian women in altering the outcome of the results. The capsules, free from the

drug, given to control cases were not real placebo as they did not have the mercapto odor. The subjects, however, were medically unsophisticated and had no knowledge that the DMPS capsules possessed any specific odor. Hence, the DMPS-free capsules used for the control cases may be considered as true placebo. Standardized dose of 100 mg 4 times a day rather than an individual calculation on the basis of weight or surface areas was selected as appropriate to community dispensing practices since all subjects weighed between 40–56 kg. The method of As analysis was previously validated but was not included in this investigation.

Pigmentation and keratosis are the most consistent, nonmalignant features of chronic arsenicosis. Pigmentation is not histologically related to arsenical hyperkeratosis. It has been reported to decrease following prolonged intake of As-free water (7). Our study demonstrated a significant improvement of this parameter (which is an objective one) following the intake of DMPS compared to placebo, substantiating the validity of our observation on its efficacy in the treatment of chronic arsenicosis.

It is difficult to explain why DMPS was found to show some clinical improvement while DMSA did not. DMPS is considered a more effective chelater than DMSA as the former is distributed both extra- and intracellularly (23–25). In contrast to the DMSA study, there was a small increase in urinary As compared to baseline at the beginning of each week of DMPS treatment. It is known that prolonged exposure of As causes its accumulation to various organs and tissues of the body (4,5,40). The continued increases in urine As provide a rationale for consideration of a trial of prolonged treatment with DMPS.

This highly preliminary finding of a promising and effective treatment of epidemic arsenicosis with DMPS supports further study of this agent in a more stringent, double-blind, placebo-controlled method. Therapy might be prolonged for a minimum of 6 months. Inclusion of a larger number of cases with true randomization would possibly overcome any probable age and sex biases. The administered dose, calculated on the basis of body weight or surface area, could be more precise.

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REFERENCES

1. Guha Mazumder, D.N.; Chakraborty, A.K.; Ghosh, A.; Gupta, J.D.; Chakraborty, D.P.; Dey, S.B.; Chattopadhyay, N. Chronic Arsenic Toxicity from Drinking Tube Well Water in Rural West Bengal. Bull. World Health Organ. **1988**, *66* (4), 499–506.
2. Guha Mazumder, D.N.; Das Gupta, J.; Santra, A.; Pal, A.; Ghosh, A.; Sarkar, S. Chronic Arsenic Toxicity in West Bengal: The Worst Calamity in the World. J. Indian Med. Assoc. **1998**, *96*, 4–7.
3. UNICEF. Plan of Action to Combat Situation Arising Out of Arsenic Contamination in Drinking Water: Plan to Assist Govt. of West Bengal. Calcutta: UNICEF, Calcutta. 1998: 5–6.
4. Guha Mazumder, D.N.; Das Gupta, J.; Santra, A.; Pal, A.; Ghosh, A.; Sarkar, S.; Chattopadhyeya, N.; Chakraborti, D. Non-cancer Effects of Chronic Arsenicosis with Special Reference to Liver Damage. In *Arsenic: Exposure and Health Effects*; Abernathy C.O., Calderon, R.L., Chappell, W.R., Eds.; Chapman & Hall: London, 1997; 112–123.
5. National Research Council. Arsenic in Drinking Water. Washington DC, National Academy Press. 1999: 130.
6. Arguello, R.A.; Cenget, D.; Tello, E.E. Cancer and Endemic Arsenism in the Cordoba Region. Rev. Argent. Dermanosifilogr. **1938**, *22*, 461–487.
7. Guha Mazumder, D.N.; De, B.K.; Santra, A.; Dasgupta, J.; Ghosh, N.; Roy, B.R.; Ghossal, U.C.; Saha, J.; Chatterjee, A.; Dutta, S.; Hague, R.; Smith, A.H.; Chakraborti, D.; Angle, C.R.; Centeno, J.A. Chronic Arsenic Toxicity: Epidemiology, Natural History, and Treatment. In *Arsenic Exposure and Health Effect*; Chappell, W.R., Abernathy, C.O., Calderon, R.L., Eds.; Elsevier Science Ltd.: New York, 1999; 335–347.
8. Peters, R.A.; Stocken, L.A.; Thompson, R.H.S. British Anti-Lewisite (BAL). Nature **1945**, *156*, 616–619.
9. Petrunkin, V.E. Synthesis and Properties of Dimercapto Derivatives of Alkylsulfonic Acid. Ukr. Khem. Zh. **1956**, *22*, 603–607.
10. Liang, Y.I.; Chu, C.C.; Tsen, Y.L.; Ting, K.S. Studies on Antibilharzial Drugs. VI. The Antidotal Effects of Sodium Dimercaptosuccinate and BAL-Glucoside Against Tartar Emetic. Acta Physiol. Sin. **1957**, *21*, 24–32.
11. Inns, R.H.; Rice, P.; Bright, J.E.; Marrs, T.C. Evaluation of the Efficacy of Dimercapto Chelating Agents for the Treatment of Systemic Organic Arsenic Poisoning in Rabbits. Hum. Exp. Toxicol. **1990**, *9*, 215–220.
12. Inns, R.H.; Rice, P. Efficacy of Dimercapto Chelating Agents for the Treatment of Poisoning by Percutaneously Applied Dichloro (2-Chlorovinyl) Arsine in Rabbits. Hum. Exp. Toxicol. **1993**, *12*, 241–246.

13. Kreppel, H.; Paepcke, U.; Thiermann, H.; Szinicz, L.; Reichl, F.X.; Singh, P.K.; Jones, M.M. Therapeutic Efficacy of New Dimercaptosuccinic Acid (DMSA) Analogues in Acute Arsenic Trioxide Poisoning in Mice. Arch. Toxicol. **1993**, *67* (8), 580–585.
14. KreppeL, H.; Reichl, F.X.; Szinicz, L.; Fichtl, B.; Forth, W. Efficacy of Various Dithiol Compounds in Acute Arsenic Poisoning in Mice. Arch. Toxicol. **1990**, *64*, 384–392.
15. Reichl, F.X.; Kreppel, H.; Forth, W. Pyruvate and Lactate Metabolism in Livers of Guinea Pigs Perfused with Chelating Agents After Repeated Treatment with AS_2O_3. Arch. Toxicol. **1991**, *65*, 235–238.
16. Aposhian, H.V.; Maiorino, R.M.; Gonzalex-Kamirez, D.; Zuniga-Charles, M.; Xu, Z.; Hurlbat, K.M.; Juneo-Munoz, P.; Dart, R.C.; Aposhian, M.M. Mobilization of Heavy Metals by Newer, Therapeutically Useful Chelating Agents. Toxicology **1995**, *97*, 23–38.
17. Guha Mazumder, D.N.; Ghoshal, U.C.; Saha, J.; Santra, A.; De, B.K.; Chatterjee, A.; Dutta, S.; Angle, C.R.; Centeno, J.A. Randomized Placebo Controlled Trial of 2,3-Dimercaptosuccinic Acid in Therapy of Chronic Arsenicosis Due to Drinking Arsenic Contaminated Subsoil Water. J. Toxicol. Clin. Toxicol. **1998**, *36*, 683–690.
18. Atallah, R.; Kalman, D.A. On-Line Photo-Oxidation for the Determination of Organoarsenic Compounds by Atomic Absorption Spectrometry with Continuous Arsine Generation. Talanta **1991**, *38*, 167–173.
19. Kosnett, M.J. Clinical Approaches to the Treatment of Chronic Arsenic Intoxication. From Chelation to Chemoprevention. In *Arsenic Exposure and Health Effects*; Chappell, W.R., Abernathy, C.O., Caldern, R.L., Eds.; Elsevier Science Ltd.: New York, 1999; 349–354.
20. Eagle, H.; Magnuson, H.J. The Systemic Treatment of 227 Cases of Arsenic Poisoning (Encephalitis, Dermatitis, Blood Dyscrasias, Jaundice, Fever) with 2,3-Dimercaptopropanol (BAL). Am. J. Syph. Gom. V.D. **1946**, *30*, 420–441.
21. Aposhian, H.V.; Arroyo, A.; Cebrian, M.E.; del Raeo, L.M.; Hurlbut, K.M.; Dart, R.C.; Gonzalez-Ramirez, D.; Kreppel, H.; Speisky, H.; Smith, A.; Gonsebatt, M.E.; Ostrosky-Wegman, P.; Aposhian, M.M. DMPS—Arsenic Challenge Test. I. Increased Urinary Excretion of Monomethylarsonic Acid in Humans Given Dimercaptopropane Sulfonate. J. Pharmacol. Exp. Ther. **1997**, *282*, 192–200.
22. Maiorino, R.M.; Dart, R.C.; Carter, D.E.; Aposhian, H.V. Determination and Metabolism of Dithiol Chelating Agent. XII. Metabolism and Pharmacokinetics of Sodium 2,3-Dimercaptopropane-1-sulfonate in Humans. J. Pharmacol. Exp. Ther. **1991**, *259*, 808–814.
23. Zheng, W.; Maiorino, R.M.; Brendel, K.; Aposhian, H.V. Determination and Metabolism of Dithiol Chelating Agents. VII. Biliary Excretion of Dithiols and Their Interactions with Cadmium and Metallothionein. Fund. Appl. Toxicol. **1990**, *14*, 598–607.
24. Wildenauer, D.B.; Reuther, H.; Weger, N. Interactions of the Chelating Agent 2,3-Dimercaptopropane-1-sulfonate with Red Blood Cells in Vitro. I. Evidence for Carrier Mediated Transport. Chem. Biol. Interact. **1982**, *42*, 165–177.
25. Reuther, H.; Wildenauer, D.B.; Weger, N. Interactions of the Chelating Agent 2,3-Dimercaptopropane-1-sulfonate with Red Blood Cells in Vitro. II. Effects on Metalloproteins. Chemico. Biol. Interact. **1982**, *42*, 179–194.
26. Domingo, J.L. Metal-Induced Developmental Toxicity in Mammals: A Review. J. Toxicol. Environ. Health **1994**, *42*, 123–141.
27. Jones, M.M.; Basinger, M.A. A Hypothesis for the Selection of Chelate Antidotes for Toxic Metals. Med. Hypotheses **1982**, *9*, 445–453.
28. Lazareva, V.I.; Lazarev, A.I. Spectrophotometric Determination of Ruthenium with Unithiol. Indus. Lab. USSR **1986**, *51*, 1075–1080.
29. Usatenko, Y.I.; Klimovich, E.A.; Loshkarev, Y.M. Amperometric Titration of Mercury Using a Unithiol Solution. Ukrainski. Khimicheskii. Zh. **1961**, *27*, 823–827.
30. O'Connor, R.J.; McGown, E.L.; Dill, K.; Hallowell, S.F. Relative Binding Constants of Arsenical-Antidote Adducts Determined by NMR Spectroscopy. Res. Commun. Chem. Pathol. Pharmacol. **1990**, *69*, 365–368.
31. Jones, M.M. Therapeutic Chelating Agents. In *Metal Ions in Biological Systems*; Siegel, H., Ed.; Marcel Dekker: New York, 1983; Vol. 16, 47–82.
32. Parr, W. Process for Producing of 2,3-Dimercaptopropane-1-sulfonic Acid and Its Salts. US Patent **1983**, 4382 040.
33. Bennett, D.W.; Huang, L.; Dill, K. Semiempirical Self-Consistent Field (CNDO) Calculation of Arsenical-Antidotes Adducts. Chem. Res. Toxicol. **1992**, *5*, 5–7.
34. Dou, Y.; McHugh, T.; Lane, W.V.; Rossant, C.J.; Loring, R.H. Interactions of Dithiols with p-Aminophenyldichloroarsine and Nicotinic Acetylcholine Receptors. J. Biol. Chem. **1994**, *269*, 20,410–20,416.
35. O'Connor, R.J.; McGown, E.L.; Dill, K. Two-Dimensional NMR Studies of Arsenic-Sulfhydryl Adducts. Mag. Reson. Chem. **1989**, *27*, 669–675.
36. Campbell, J.R.; Clarkson, T.W.; Omar, M.D. The Therapeutic Use of 2,3-Dimercaptopropane-1-sulfonate in Two Cases of Inorganic Mercury Poisoning. Am. J. Med. Assoc. **1986**, *256*, 3127–3130.
37. Chisholm, J.J., Jr.; Thomas, D.J. Use of 2,3-Dimercaptopropane-1-sulfonate in Treatment of Lead Poisoning in Children. J. Pharmacol. Exp. Ther. **1985**, *235*, 665–669.
38. Kew, J.; Morris, C.; Aihie, A.; Fysh, R.; Jones, S.; Brooks, D. Arsenic and Mercury Intoxication Due to Indian Ethnic Remedies. Br. Med. J. **1993**, *306*, 506–507.
39. Moore, D.F.; O'Callaghan, C.A.; Berlyne, G.; Ogg, C.S.; Davies, H.A.; House, I.M.; Henry, J.A. Acute Arsenic Poisoning: Absence of Polyneuropathy After Treatment with 2,3-Dimercaptopropanesulphonate (DMPS). J. Neurol. Neurosurg. Psychiatry **1994**, *57*, 1133–1135.
40. Scott, A. The Retention of Arsenic in the Late Cutaneous Complications of Its Adminstration. Br. J. Dermatol. **1958**, *70*, 195–200.