DMPS-Arsenic Challenge Test. I: Increased Urinary Excretion of Monomethylarsonic Acid in Humans Given Dimercaptopropane Sulfonate

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ABSTRACT

The purpose of the present study was to evaluate in a novel manner the arsenic exposure of humans living in two towns in Northeastern Chile. Residents of one town drink water containing 593 μg As/l. Those in the control town drink water containing 21 μg As/l. Our hypothesis was that the administration of the chelating agent, 2,3-dimercaptopropane-1-sulfonic acid, Na salt (DMPS, DIMAVAL) would increase the urinary excretion of arsenic, alter the urinary profile of arsenic species and thus result in a better indication of the body load of arsenic and a better biomarker for arsenic exposure. The method used to evaluate these subjects was to give them 300 mg DMPS by mouth, after an overnight fast, and collect urine at specified time periods. The urine samples were analyzed for inorganic arsenic, monomethylarsonic acid (MMA), dimethylarsinic acid (DMA) and total arsenic by hydride generation and atomic absorption spectrophotometry. The results indicated that: 1) During the 2-hr period after DMPS administration, MMA representation 42%, inorganic As, 20 to 22% and DMA, 37 to 38% of the total urinary arsenic. The usual range of the MMA percentage in human urine has been 10 to 20%. The % MMA increased almost equally for both the arsenic-exposed and control subjects. 2) The exposed subjects had a greater urinary excretion of total arsenic, before and after DMPS administration, than the control subjects. 3) Although buccal cells were obtained only from a few subjects, the prevalence of mononucleated buccal cells, an indication of genotoxicity, was 5-fold greater for those who consumed drinking water with the higher arsenic content than among control subjects. Our conclusions are that 1) DMPS has a highly specific effect in humans on MMA metabolism and/or urinary excretion; 2) the human body stores substantial amounts of arsenic; and 3) the urinary arsenic concentration after DMPS administration may be more indicative of the body burden of arsenic because it was greater than that found before DMPS was given.

Epidemiological evidence indicates that ingestion of arsenic compounds via drinking water can result in skin cancer and cancer of internal organs (Chen et al., 1985), whereas exposure via inhalation can lead to cancer of the lungs (IARC, 1980). These carcinogenic results of arsenic exposure have been observed only in the human. Animal models have been reported but are, to say the least, questionable. The drinking of water containing high levels of inorganic arsenic by humans has continued to be of concern at the local and international level. For example, arsenic in the drinking water from the deep artesian wells of Southwest Taiwan has been implicated in the etiology of Blackfoot Disease, a vascular disease, which can result in spontaneous or surgical amputation of limbs (Tseng, 1977). The etiology of this disease is controversial, even among Taiwanese investigators (Tseng et al., 1996; Chen et al., 1995). Recent reports indicate that the drinking water from an area where Blackfoot Disease is endemic is different from two control areas in its content of insoluble arsenic and not in its soluble arsenic (Chen et al., 1995). There have been other investigations of populations who drink water with high arsenate/arsenite levels in Chile (Sancho et al., 1992), Mexico (Cebrian et al.,

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ABBREVIATIONS: DMPS, sodium 2,3-dimercaptop-1-propane sulfonate; inorgAs, inorganic arsenic; MMA, monomethylarsonic acid; DMA, dimethylarsinic acid; TotAs, total arsenic = inorg As + MMA + DMA; MN, micronuclei.
1983) and most recently in India (Guha Mazumder et al., 1988).

In West Bengal, India, more than 800,000 people have been
reported to be drinking water containing 190 to 737 μg
arsenic per liter with 175,000 of them showing open lesions
related to arsenic exposure (Guha Mazumder et al., 1988;
Chatterjee et al., 1995).

In 1994, the Tucson group was asked to study a group
of residents of San Pedro de Atacama, Chile who were believed
to drink water containing approximately 600 μg As/l. The
WHO (1996) recommendation is that arsenic in drinking
water should not exceed 10 μg As/l. This population in North-
eastern Chile does not have a high incidence of arsenic-
related diseases. Neither Blackfoot Disease nor skin cancer
has been detected (personal communication, A. Arroyo).
Because of our extensive experience with chelating agents
(Aposhian, 1983; Aposhian and Aposhian, 1990; Aposhian et
al., 1995; Gonzalez-Ramirez et al., 1995; Maiorino et al., 1996),
especially with the sodium salt of 2,3-dimercaptopro-
pane-1-sulfonic acid (DMPS, DIMAVAL), it was decided to
use this orally active chelating agent to answer four ques-
tions. First, will DMPS, an effective mobilizing agent for
mercury in humans (Aposhian et al., 1992; Gonzalez-Ramirez
et al., 1995; Maiorino et al., 1996; reviewed by Aaseth et al.,
1995; Aposhian et al., 1995), mobilize arsenic in humans
exposed to inorganic arsenic in their drinking water? Second,
is arsenic stored in the human body? Third, will the use of
DMPS give a more accurate estimate of the body burden
of arsenic in humans? Fourth, do subjects from the exposed
town have a body burden of arsenic greater than those from
the control town? The results of these studies indicate that
the answers to all of these questions are positive. In addition,
MMA, which was approximately 14% of the total urinary
arsenic before DMPS, increased to 42% during the 2-hr pe-
riod after DMPS administration. This large MMA percentage
in the urine is most unusual for humans.

Materials and Methods

Clinical. Subjects underwent a history and physical examination
before enrollment in the study. Female subjects were given a urinary
pregnancy test and if positive were disqualified as subjects. The
physical examination was repeated 24 hr after DMPS administra-
tion. DIMAVAL capsules of the same lot number containing 100 mg
DMPS were used in this study and were gifts of Heyl (Berlin,
Germany). In Germany, DIMAVAL is registered with the German equi-
valent of the U.S. Food and Drug Administration. DIMAVAL is the
only DMPS preparation that is prepared by acceptable Western
World pharmaceutical manufacturing procedures.

Our experimental protocol was approved by the Ethics Commit-
tees of the Republic of Chile, Ministry of Health, Health Service
Antofagasta, Department of Integrated Attentions to Persons and
the University of Chile. Because DIMAVAL is an investigational
drug in the United States, the study was performed under the U.S.
Food and Drug Administration IND No. 34,682.

Vital brand purified bottle water was used for drinking water
during the study. The source was a thermal fountain in Chan-
queahue in the Sixth Region of Chile. Before being bottle,
the water was purified with porcelain and membrane filters. The most perni-
cent characteristic of this commercially available water was that the
arsenic concentration was less than 0.05 mg/l.

Protocol for the DMPS chelation test. Participants were asked
to exclude seafood from their diet for the preceding 3 days. Before
DMPS administration, each participant read and signed a consent
form, which was written in Spanish. A brief medical and occupa-
tional questionnaire for each subject was filled out by the interviewer
after questioning the subject. Inclusion criteria for this study were:
adults, 18 to 69 years of age. Exclusion criteria were: subjects with
known hypersensitivity to similar chemical chelating agents, sub-
jects with a history of previous chelation therapy, subjects with a
history of current physical findings of serious renal or psychiatric
disease, subjects with abnormalities in blood tests or urinalysis that
in the investigator’s opinion would interfere with the evaluation of
safety data, subjects who had received any investigational drug
during the preceding month before the initiation of this study; sub-
jects who had taken drugs with well-defined organ toxicity within
the past 6 months, subjects who were pregnant or lactating, subjects
with a history of alcohol or recreational drug abuse and subjects who
were not capable of giving informed consent.

Subjects were fasted overnight (minus 11 to 0 hr) before DMPS
administration (table 1) during which time they were allowed to
drink purified bottled water. Throughout the study, the subjects
drank Vital brand purified bottled water. At 0 hr (beginning at 7
A.M.) they were given 300 mg DMPS and encouraged to drink 500 ml
purified water. They received no food until 4 hr after DMPS admin-
istration, at which time they were given a chicken sandwich and a
banana. Urine was collected from 11 hr before the time of DMPS
administration and for the following 24 hr according to a predeter-
ned schedule (table 1). The DMPS dose was chosen on the basis of
previous studies at The University of Arizona (Maiorino et al., 1991;
Aposhian et al., 1992) and other clinical reports (Kemper et al., 1990).
This dose was given to each subject independent of the body weight
because the protocol was a diagnostic test, not a treatment for
toxicity.

Urine collection. All collecting containers had been soaked over-
night in 2% nitric acid (Baker analyzed for trace metal analysis) or
exposed in 20% nitric acid and rinsed with water that had been
double distilled and deionized. All plastic measuring and collecting
equipment were so washed in Tucson, AZ, sealed in bags, placed
in locked foot lockers and transported by air to the site of the study at
the same time as the investigators. Urine was collected in a 3-liter
polyethylene container (Baxter Laboratories, Inc., Morton Grove,
IL); the volume was measured; pH adjusted to 4 to 5 by adding
concentrated HCl (Baker analyzed for trace metal analysis); and
immediately frozen by placing in a portable icebox containing dry ice.
The samples were kept frozen while being transported to Tucson,
where they were stored at −20°C for approximately 6 months. At
that time, they were thawed by standing at room temperature over-
night. The next morning, the samples were mixed by five gentle
inversions, 35 ml were transferred to acid-washed plastic containers,
quick-frozen and carried frozen by air to Mexico City, where they

| TABLE 1
<table>
<thead>
<tr>
<th>DMPS-arsenic challenge protocol</th>
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<tr>
<td>−11 to 0 hr</td>
</tr>
<tr>
<td>Begin overnight urine collection</td>
</tr>
<tr>
<td>0 hr</td>
</tr>
<tr>
<td>No breakfast, no coffee, no tea</td>
</tr>
<tr>
<td>Administer three 100-mg DMPS capsules</td>
</tr>
<tr>
<td>Begin 0–2 hr urine collection</td>
</tr>
<tr>
<td>2 hr</td>
</tr>
<tr>
<td>Begin 2–4 hr urine collection</td>
</tr>
<tr>
<td>4 hr</td>
</tr>
<tr>
<td>Begin 4–6 hr urine collection</td>
</tr>
<tr>
<td>Chicken sandwich</td>
</tr>
<tr>
<td>6 hr</td>
</tr>
<tr>
<td>Begin 6–24 hr urine collection</td>
</tr>
<tr>
<td>11 hr</td>
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<td>24 hr</td>
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Physical examinations were given and vital signs were measured before and after the study.
were analyzed in the CINVESTAV Laboratory for arsenic species by hydride generation atomic absorption spectrophotometry. The analyst did not know the identity of the samples or the village from which they were obtained.

**Total arsenic analysis.** An aliquot of urine (0.5–3.0 ml) was wet digested with nitric, sulfuric and perchloric acids according to Cox (1980). All digested samples were pretreated at room temperature with 0.5 ml of 10% (w/v) potassium iodide solution and 2.5% (w/v) ascorbic acid solution for 0.5 hr before measurement. Digested urine samples were analyzed in a Perkin Elmer 3100 atomic absorption spectrophotometer equipped with a flow injection atomic spectroscopy system (FIAS-200). All measurements were made with an arsenic electrodeless discharge lamp. The detection limit of this technique for total arsenic is 5 μg/l.

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. Argon was the carrier gas.

**Arsenic species analysis.** Aliquots of urine samples were digested with 2 M hydrochloric acid for 5 hr at 80°C. Arsenic species were separated according to Crecelius (1986). Arsenicals were reduced to their corresponding hydrides and then detected with use of a Varian model 475 atomic absorption spectrophotometer. In the procedure, inorgAs, MMA and DMA were selectively reduced to the gaseous compounds arsine, methylarsine and dimethylarsine by controlled pH and with sodium borohydride as a reducing agent. Arsines were then trapped in a liquid nitrogen-cooled chromatographic trap, which upon warming, allowed a separation of arsenic species based on boiling points. The released arsines were swept by helium carrier gas into a quartz cuvette burner cell, where they were decomposed to atomic arsenic. The system was calibrated by the analysis of standards that contained inorgAs (+5), MMA (+5) and DMA (+5). Because standard urine containing known amounts of As species was not available commercially, the reliability of the separation procedures was assessed by spiking urine samples with known amounts of inorgAs, MMA and DMA (20:20:60), so that three different concentrations (45, 420 and 1150 μg/l) of TotAs could be analyzed (Vahter and Lind, 1986). Recoveries ranged from 92 to 114% with coefficients of variation between 0.5 and 12%. Freeze-dried urine standard reference material for toxic metals (SRM 2670, National Institute of Standards and Technology [NIST], Gaithersburg, MD) was analyzed for TotAs. The certified concentration of the standard was 480 μg As/l. We obtained 511 μg As/l (range, 431–545). Our accuracy was 90 to 113%. In addition, the laboratory participates in the laboratory intercomparisons program for As speciation in human urine, which is coordinated by Dr. E. Crecelius, Battelle, Marine Sciences Laboratory, Pacific Northwest Division, Sequim, WA. Our detection limit for arsenic species was 1 ng for inorgAs, 2 ng for MMA and 4 ng for DMA. The results obtained had an accuracy of 90 to 108% and 2 to 13% coefficient of variation.

Analysis of total arsenic in water was carried out as reported previously (Del Razo et al., 1990). For quality control purposes, the Standard Reference Water (1643c, NIST) was analyzed for TotAs (certified concentration 82.1 ± 1.2 μg As/l) at the same time as the collected water samples. The results obtained had an accuracy of 95 to 105% and 2 to 7% coefficient of variation.

**Creatinine in urine.** Creatinine was determined by a colorimetric automated method with use of a Vitalab Eclipse, Merck spectrophotometer. Arsenic concentrations in urine were expressed as micrograms per gram of creatinine.

**Micronuclei assay.** Buccal cells were collected by gently rubbing the inside of the mouth with a premoistened wooden applicator, which was then dipped into isotonic saline solution in a 15-ml plastic centrifuge tube. The cells were allowed to fall into the solution and gently pipetted to reduce cell clumping. The test tubes were kept on ice after they were collected and transported by air in a small camping icebox containing ice to Mexico City, Mexico with one of the investigators. The cells were centrifuged for 10 min at 200 × g, fixed with methanol for 1 hr and placed on a clean glass slide. Slides were air dried and preparations were Feulgen-stained by pretreatment with 1 N HCl for 5 min at room temperature, placed for 6 min in 1 N HCl at 60°C, rinsed with distilled water, put into Schiff’s reagent for 60 to 90 min and rinsed in tap water. The presence of micronucleated cells was confirmed by three different analysts with the criteria described by Tolbert et al. (1992). The analysts did not know whether they were examining buccal preparations from San Pedro de Atacama or Toconao.

**Results**

**Site of study.** San Pedro de Atacama was our study town. Toconao was the control town. They are relatively isolated in the Atacama Desert in northeast Chile, more specifically in the El Loa Province of the Second Region (Antofagasta Region) of Chile (fig. 1). San Pedro de Atacama is a 5- to 6-hr automobile drive from the city of Antofagasta, is approximately 2437 meters above sea level and is situated on the banks of the Vilama and San Pedro Rivers. The Vilama River has an arsenic concentration of 593 μg/l, and the San Pedro River, 220 μg/l. This is the average of monthly analyses performed by the Health Services Laboratory of the Second Region. This is not an anthropogenic pollution. It is believed that the water has contained high levels of arsenic for centuries and that the source of the arsenic in the area is the runoff from high volcanic formations. In addition, the arsenic content of the water has seasonal variations. Toconao is approximately 1-hr drive beyond San Pedro de Atacama and is 2477 meters above sea level. In Toconao, the people drink water from the Onar-Jerez Creek (19 μg As/l) and the Silapeti River (15 μg As/l).

There is a rudimentary medical dispensary in each of these towns. They are in contact by radio, when necessary, with the Regional Health Department located in the city of Antofagasta. The most common diseases are acute respiratory diseases in the winter and acute enteric diseases in the summer. The medical dispensary of each town was where the physical examinations of each subject were performed, DMPS administered and urine collected and measured. The Secretary of Health for the Second Region is Dr. Alex Arroyo-Meneses, whose medical specialty is dermatology and who is still active in the practice of this specialty.

The local economies of San Pedro de Atacama and Toconao are based, in order of their importance, on agriculture, tourism and craftsmanship. In addition, Toconao has two other industries, lithium mining and extraction and the extraction of mineral salts such as KCl and borates.

The main environmental problems of the two towns are that the drinking water must be highly chlorinated because of its source and the absence of a sewerage system. In addition, San Pedro de Atacama lacks a garbage treatment facility.

**Demographics.** The population of the two towns is mostly of Aymara and Quechua ethnic native Chilean heritage, whose ancestors have lived in the area for 11,000 years (Núñez-Atlencio et al., 1991). Volunteers were chosen from San Pedro de Atacama from those who were drinking at least some water from the water source having a high level of arsenic. These subjects were known from a previous study to have high arsenic levels in their urine (Hopenhayn-Rich et al., 1996). Volunteers were also selected from Toconao, the control town. Sex and age matching was attempted (table 2). Six men were included from each town, but an equal number
of women from each town was not obtained because there was an insufficient number of women volunteers from the control town. Other demographics are summarized in table 2.

**Arsenic concentration of drinking water.** Samples of San Pedro de Atacama and Toconao tap water, collected and analyzed for TotAs at the same time as the urine samples, contained 528 and 19.1 μg As/l, respectively (table 2). Recent reports by the Second District Government state that the drinking water of San Pedro de Atacama and Toconao contain 593 and 21 μg/l TotAs, respectively. The concentration of water removed from the San Pedro River water at the time of the study was determined to be 124 μg/l.

**Concentration of arsenic species in the urine samples.** The concentrations of TotAs (μg/g creatinine) excreted in the urine before and after the DMPS challenge were much greater in the subjects from San Pedro de Atacama than in those from the control town of Toconao at all time intervals (fig. 2). For both groups, the concentrations of each As species in the urine samples were the greatest during the 0- to 2-hr period (fig. 3), and did not return to the concentrations of the species found before the DMPS challenge.

Before DMPS administration, the urinary mean inorgAs concentration was approximately six times greater for the San Pedro de Atacama group than for the Toconao group. It was 7, 5, 7 and 9 times greater at 0 to 2, 2 to 4, 4 to 6 and 6 to 24 hr, respectively. The concentration values are included because toxicology is usually concerned with concentrations.

When the inorgAs concentrations before and 0 to 2 hr after the DMPS challenge were compared, DMPS increased the concentration 4.4- and 5.3-fold for the Toconao and San Pedro de Atacama subjects, respectively. For MMA, the concentration increased 11.9- and 10.2-fold, respectively, and for DMA, only 1.7- and 1.9-fold, respectively. There was good agreement between the summation of inorgAs + MMA + DMA with TotAs (table 3).

**Amount of arsenic species in the urine samples.** Of even greater interest than the concentrations were the amounts of
the various arsenic species in the urine after the DMPS challenge because they are a better indicator of the body burden of arsenic. The mean TotAs in the urine of the San Pedro de Atacama subjects increased approximately 4-fold during the 2-hr period after DMPS administration, as compared with the preceding 2-hr period (fig. 4). When the San Pedro de Atacama and Toconao subjects were compared, there was a striking difference noted between the mean amount of TotAs excreted in the urine during all time periods (fig. 4).

In addition, the administration of DMPS resulted in a marked increase in the amount of urinary MMA of both the San Pedro and Toconao groups (fig. 5). There was approximately a 9-fold increase in urinary MMA during the 2-hr period after DMPS administration as compared with the previous 2 hr. For the same time periods, urinary inorgAs was increased about 5-fold and DMA less than 2-fold. From 2 to 6 hr after DMPS, the amount of inorgAs, MMA and DMA did not change to any great extent.

For the Toconao subjects, although the absolute amounts of arsenic species per 2-hr period were much less, the fold increases relative to the preceding time period were similar.

**Percent of arsenic species in the urine.** The percent inorgAs in the urine increased after DMPS administration (fig. 6). For MMA, it increased from 15% (San Pedro de Atacama) and 12% (Toconao) before DMPS administration to 42% for each group during the 0- to 2-hr period after DMPS. By the end of 6 hr, it had decreased to 28 and 24% for San Pedro de Atacama and Toconao groups, respectively. For DMA, however, the percentage decreased after DMPS. Although DMPS administration resulted in significant changes in the percent of these various arsenic species excreted in the urine of both San Pedro de Atacama and Toconao subjects, the magnitude of the changes in relative percent were essentially the same for both groups (fig. 6).

The lowest MMA percentage for an individual of the Toconao group was 3.9% before DMPS, which became 39.4% for the 0 to 2 hr after DMPS administration. For the San Pedro de Atacama group, the lowest MMA percentage for an individual was 8.4%, which became 53.9% for the 0 to 2 hr after DMPS administration. Vahter *et al.* (1995a) reported that the mean percentage of MMA excretion in the urine of an unusual group of native Andean women, some drinking water high and others low in arsenic content, was 2.2 and 3.5%, respectively, with the range of 0.6 to 8.3 and 0.0 to 11.

The lowest DMA percentage of an individual of the Toconao group was 35.2% before DMPS, which became 26.2% 0 to 2 hr after DMPS administration vs. 42.6% and 12.1% for the individual with lowest percentage of the San Pedro de Atacama group.

**Genotoxicity study.** The prevalence of micronucleated cells among the San Pedro de Atacama subjects \((n = 9)\) was 5-fold greater than that observed among the Toconao sub-

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**Fig. 2.** Total arsenic concentration in urine before and after administration of 300 mg DMPS. DMPS was given p.o. at time 0. Error bars in this and other figures represent ± S.E.

**Fig. 3.** Concentration of arsenic species in the urine, \(\mu g/g\) creatinine, before and after 300 mg DMPS administration p.o. (A) San Pedro de Atacama subjects; (B) Toconao subjects.
arsenic was greater than that indicated by the urinary urine after DMPS administration and that the body burden demonstrated that substantially more arsenic was excreted in the body burden of arsenic. The DMPS challenge test dem-

(1990) indicated, however, that 40 to 60% of the arsenic is not stored in the body. Farmer and Johnson et al. (1995a, b; Healy et al., 1997). 1) DMPS may inhibit the methyltransferase activity that methylates MMA to produce DMA, which results in the accumulation of MMA in the body and urine with less DMA being available for urinary excretion. But DMPS at concentrations of 1 to 10 μM did not inhibit a 2800-fold purified rabbit liver arsenite or MMA methyltransferase in vitro (Zakharyan, personal communication) assayed in the presence of 3.3 mM GSH under the conditions described by Zakharyan et al. (1995). Neither could 10 to 40 μM DMPS replace GSH as a required thiol in these assays. These DMPS concentrations are in the range of those found in human blood after a DMPS challenge test (Maiorino et al., 1991). Buchet and Lauwerys (1988), however, reported that 0.05 to 0.5 mM DMPS almost completely abolished the methylation reaction by a rat liver cytosol preparation, but it was not clear whether the assay was performed with or without GSH. 2) DMPS with its two thiol groups may have chemically reduced arsenate to arsen-
ite in vivo and thus more MMA was synthesized and made available for excretion. 3) The reducing environment produced by DMPS may have stimulated in some manner the mechanisms involved in the urinary excretion of MMA but not DMA. 4) MMA containing As$^{+++}$ may be stored in the human body before excretion. If so, DMPS may have reduced it to MMA containing As$^{++}$, which appears to be more chelatable by DMPS, or the DMPS may have chelated this elusive species of MMA containing As$^{++}$ and thus increased its excretion. Such a trivalent form has been postulated but never isolated from in vivo or in vitro studies. In support of this, to some extent, is that when the urine samples were not first digested with 2 M HCl, the summation of the separately determined inorgAs + MMA + DMA by the method of Crecelius (1986) was about 60% lower than the experimentally determined total arsenic. It is for this reason that the arsenic species analyses of this paper were performed after digestion with 2 M HCl. With this relatively gentle digestion procedure, there was good agreement between the summation of inorgAs + MMA + DMA with TotAs. These irregularities did not occur when −11 to 0 hr urine samples were analyzed, because they were collected before DMPS had been administered. In addition, when four of the urine samples of this study were analyzed by high-performance liquid chromatography-inductively coupled plasma-mass spectrometry, a broad new unidentified peak overlapping the MMA peak was found in urine samples collected after DMPS administration (K. Irgolic and W. Goessler, personal communication). This peak disappeared on acid treatment of the urine. Whether this new peak is or is not the DMPS-As chelate has not been established. No other information about the structure of this unidentified peak is currently available.

It should be noted that the percentage of inorgAs also increased after DMPS administration, but the rate of increase and the magnitude of the increase were not as great as that for MMA. An inorgAs change of this magnitude is unusual in humans but has been reported also by Del Razo et al. (1997).

The subjects for the present study were part of a larger group of 122 people from San Pedro de Atacama and 98 from Toconao who had been studied previously by Hopenhayn-Rich et al. (1996). In the previous study, the MMA/DMA ratio was 1.5 times greater in the group drinking water with a high arsenic content. This was true also in the present study for the −11 to 0-hr urine, that is, before DMPS administration.

When DMPS was given intramuscularly to rabbits after a subcutaneous injection of arsenite, an increased MMA but not DMA excretion was also noted (Maiorino and Aposhian, 1985), which again demonstrates the value of the rabbit as a model for the human's metabolic processing of inorganic arsenic as has been suggested previously (Maiorino and Aposhian, 1985; Vahter, 1983).

An additional result of this study has genotoxic importance. This South American group had a similar genotoxic response in oral epithelial cells (table 4) to that found in
buccal smears from 33 individuals in northern Mexico who had been chronically exposed to 396 to 435 mg As/l in their drinking water (Gonsebatt et al., in press). These results, and the fact that micronuclei frequencies in exfoliated cells have been validated as tissue-specific dosimeters of carcinogen exposure in humans (Rosin, 1992), strengthens the value of this assay for the demonstration of early biological effects of arsenic exposure and could be an aid in risk assessment of known or suspected arsenic exposure.

DMPS is not a new drug, even though it is still an investigational drug in the United States. It was developed in the 1950s in the former Soviet Union and became an official drug in the Soviet physician’s armamentarium in 1958 (Aposhian, 1983). It was introduced into the Western world in 1978. Since then, it has had wide use, especially in Germany, as a chelating agent for both the diagnosis and mobilization of inorganic mercury in the body (for reviews, see Aposhian, 1983; Aposhian et al., 1995; Kemper et al., 1990; Aaseth et al., 1995). This use has been extensive because of the concerns about humans exposed to elemental mercury emitted from dental amalgams in vivo (Lorscheider et al., 1995; Aposhian et al., 1992) and dental personnel exposed occupationally to mercury (Gonzalez-Ramirez et al., 1995).

Although the present study has yielded several new and important contributions to our knowledge about arsenic exposure of humans via drinking water, and the usefulness of DMPS as a mobilizing agent for arsenic, especially for MMA, the early use of DMPS to decrease the As body burden of such subjects would appear warranted, to decrease possible cancer and genotoxicity risks.

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References


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