

Human studies with the chelating agents, DMPS and DMSA. (2,3-dimercaptopropane-1-sulfonic acid, meso-2,3-dimercaptosuccinic acid). H. Vasken Aposhian, Richard M. Maiorino, Mario Rivera, David C. Bruce, Richard C. Dart, Katherine M. Hurlbut, Deborah J. Levine, Wei Zheng, Quintus Fernando, Dean Carter and Mary M. Aposhian.

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ABSTRACT

Meso-2,3-dimercaptosuccinic acid (DMSA) is bound to plasma albumin in humans and appears to be excreted in the urine as the DMSA-cysteine mixed disulfide. The pharmacokinetics of DMSA have been determined after its administration to humans po. For the blood, the $[t_{sub,max}]$ and $t_{1/2}$ were $3.0\text{ h} + 0.45\text{ SE}$ and $3.2\text{ h} + 0.56\text{ SE}$, respectively. The $[C_{sub,max}]$ was $26.2\text{ [unkeyable]M} + 4.7\text{ SE}$. To determine whether dental amalgams influence the human body burden of mercury, we gave volunteers the sodium salt of 2,3-dimercaptopropane-1-sulfonic acid (DMPS). The diameters of dental amalgams of the subjects were determined to obtain the amalgam score. Administration of 300 mg DMPS by mouth increased the mean urinary mercury excretion of subjects over a 9 h period. There was a positive correlation between the amount of mercury excreted and the amalgam score. DMPS might be useful for increasing the urinary excretion of mercury and thus increasing the significance and reliability of this measure of mercury exposure. DMSA analogs have been designed and synthesized in attempts to increase the uptake by cell membranes of the DMSA prototype chelating agents. The iv administration of the monomethyl ester of DMSA, the dimethyl ester of DMSA or the zinc chelate of dimethyl DMSA increases the biliary excretion of platinum and cadmium in rats. (Key Words: chelating agents; pharmacokinetics, human; poisoning, human.)

INTRODUCTION

I want to thank the organizers of this workshop for the invitation to talk to you about our work with the water soluble, orally useful dimercapto chelating agents. The other night when I was trying to organize my thoughts as to what might be of interest to this group, I began to feel like the Sultan who inherited the harem. He knew what was expected of him but didn't quite know where to begin! I decided to begin by telling you about our experiments that deal with the pharmacokinetics of DMSA in humans. I will include the fate of DMSA in the blood. Second, I would like to bring you up to date on a controversy that is reaching a crescendo in Europe and is beginning in the United States. It is the concern about the safety of dental amalgams and the questionable use of chelating agents as a remedy for putative disorders resulting from dental amalgams. I shall tell you about our attempts to determine the usefulness of one of these chelating agents 2,3-dimercaptopropane- 1 sulfonate (DMPS, DIMAVAL) as a diagnostic agent for determining the body load of mercury and why we think this warrants further study. Finally, I would like to tell you about some of our work that is in progress studying a few analogs of DMSA.

The compounds that we shall be discussing are shown in Figure 1. Dimercaprol, also known as British Anti-Lewisite (BAL), is lipid soluble, is only available in peanut oil, and is not the most stable of compounds. About 50% of the patients given BAL have some adverse reactions to it. One of the advantages of DMPS and DMSA is that they are stable, crystalline materials.

They are not readily oxidized during pre-use storage. Let me also point out that because of its lipid solubility, dimercaprol can enter cells and is thus more toxic than the DMPS or DMSA. DMSA, at the

pH of the body, is ionized. Its two ionized carboxyl groups make it a very highly charged molecule. Charged molecules usually do not readily get into a cell unless there is a specific carrier or transport system. I will present experimental evidence showing that DMSA does not get into liver cells, whereas DMPS does. DMPS has been used in the Soviet Union since 1958. It has completely replaced BAL in that country and is now available in Europe as DIMAVAL. Our laboratory has an IND for human studies within the United States. I will mention also another dimercapto compound, DMPA (Figure 1), which is water soluble to some extent. It is available in crystalline form, but perhaps because of the benzene ring, it has some non-polar properties that allow it to get into a cell.

Metabolism and Pharmacokinetics of DMSA

We have been able to answer many questions about these dimercapto compounds because we have developed an assay for their determination in biological fluids [1,2]. I would like to go over this assay with you so that you will understand some terms that I shall be using. The assay depends on the reaction of bromobimane with the thiols of, for example, DMPS or DMSA (Figure 2). Bromobimane reacts with either compound to form a highly fluorescent bimane derivative. Neither bromobimane nor DMSA has such fluorescence. This fluorescence allows us to determine the presence of picomole amounts of DMSA. The terms that we use, e.g. altered, unaltered, and total DMSA, are defined in the legend of Figure 3. After we have given a subject DMSA, we collect the urine and react an aliquot of it with bromobimane. The resulting bimane derivative of DMSA is then either put on HPLC or frozen. The HPLC analysis detects unaltered DMSA which represents unchanged parent drug. Since thiol groups can be readily oxidized in the body, we take another aliquot of urine and reduce it electrolytically or if we are dealing with a blood sample, we first reduce it chemically by using dithiothreitol. The material then is reacted with bromobimane and put on HPLC to obtain total DMSA. To get altered or biotransformed DMSA, which is a calculated figure, the value of experimentally determined unaltered DMSA is subtracted from the value of experimentally determined total DMSA.

A typical urine profile from volunteers given DMSA po is shown in Figure 3. It represents an experiment using five volunteer normal male graduate students [3]. They were fasted overnight for approximately 11 h. The next morning after they received a physical examination by a physician, they were given DMSA (10 mg/kg) by mouth. Their urines were collected at various times. We determined [3,4] that 20.6% of the administered DMSA was found in the urine as total DMSA by 14 h. Very little of the administered dose was found in the urine as unaltered DMSA (2.5%). Therefore, 18.1% of the administered DMSA was changed or altered. In rabbits given DMSA, 73% of the DMSA in the urine was unaltered DMSA [5]. In humans, we found [6] that 95% of the urinary DMSA was in the form of a mixed disulfide of DMSA with two molecules of cysteine (Figure 4). The structure is being confirmed by mass spectroscopy and other means. We cannot be positive of this putative structure until Professor Fernando and his group synthesize it. Nevertheless, 95% of the DMSA found in the urine is this mixed disulfide and less than 2% is the simple disulfide form of DMSA [6].

Since we found this DMSA mixed disulfide in the urine, we expected to find the mixed disulfide in the blood. We did not. No DMSA mixed disulfide was detected in the plasma or whole blood (Figure 5). The DMSA in the blood becomes protein bound within a relatively short time (Figure 5). About 95% of the DMSA found in the blood is bound to protein. There is a small amount (<5%) of non-protein bound material (Figure 5). We don't quite know what this means at this time. It may be a cysteine-DMSA disulfide containing only one cysteine molecule, but we are not positive. At this time, we believe that this non-protein bound material is not important to what we are doing. When the plasma of subjects who received DMSA was put onto a Sephadex column, the DMSA was eluted with protein of the same molecular weight as plasma albumin [3].

Let me continue now with the pharmacokinetic parameters of DMSA in humans. Our group felt there was a need to know these parameters so that more effective therapeutic regimens could be initiated. Let me again point out that the DMSA was given po to normal human males. These pharmacokinetic values (Table 1), therefore, have some limitations that they would not have, if we had been able to give DMSA iv. Unfortunately, a parenteral preparation of DMSA is not available. After oral administration of DMSA to normal human males [3], the maximum concentration achieved in the blood ([C.sub.max]) was about 26.2 [unkeyable]molar (Table 1). Time to maximum concentration ([t.sub.max]) was about three hours (Table 1) and the elimination t_{1/2} was 3.2 h.

Before we leave this part of the talk, let me emphasize that these pharmacokinetic values were obtained using normal, healthy subjects. Whether these pharmacokinetic parameters might change in heavy metal intoxicated subjects receiving DMSA is unclear. Further studies along these lines are warranted.

We found no free DMSA and no DMSA-cysteine mixed disulfide in the blood, but we find DMSA and DMSA-mixed disulfide in the urine. What mechanisms are involved? What we are beginning to picture and hypothesize is that DMSA is in the altered form in the plasma because it is bound to albumin. DMSA must bind to the one available thiol group in a human albumin molecule. Once that disulfide link is made, we have a remaining free SH group on the DMSA molecule. Now, there are at least two possibilities. First, the other SH group on the DMSA molecule bound to the albumin molecule may be part of the active chelating moiety in the blood. Or it is also feasible that any free cysteine in the plasma binds by disulfide linkage to the remaining SH group on the albumin bound DMSA. [TABULAR DATA OMITTED]

In the kidney, it is well known that a very active thiol/disulfide exchange is possible. Our working hypothesis is that the albumin-DMSA complex travels to the kidney, where the albumin leaves a cysteine:DMSA (1:1) complex for a short period of time. (We can find a small amount of this in the urine.) The SH group of the 1:1 DMSA-cysteine complex, perhaps along with an oxygen, then becomes available for chelation. Let me point out that if you look at this 1:1 DMSA:cysteine mixed disulfide complex (Figure 4) then you have an oxygen, a nitrogen, another oxygen and a sulfur that are available for chelating a metal ion. Such atoms are prone to form chelates. We are very hopeful that this year we may be able to prove experimentally where in the molecule and where in the body chelation is taking place. We wonder whether chelation after DMSA administration goes on only in the kidney, nowhere else.

DMPS as a Challenge Test for Mercury

Let us look at these chelating agents in relation to another problem. About six or seven months ago, we were made aware of the dental amalgam controversy [7] that is going on the Europe and is beginning in Canada and this country. Since DMPS will increase the urinary excretion of mercury, it was being used by a number of physicians in Europe to diagnose mercury body loads. Since this use was being questioned by the medical establishment, we were asked to perform well controlled studies to determine in a scientific manner whether this diagnostic use had any validity. Let me first state that there are now reliable, established, respected investigators who have pointed out there may be a problem with dental amalgam [8-10]. Experiments supporting such a point of view have been published in such peer reviewed journals as the American Journal of Physiology and the FASEB Journal. Also, let me remind you that Professor Tom Clarkson, the authority on mercury intoxication, has pointed out in a number of articles that for the general population, 99% of its exposure to inorganic mercury comes from the dental amalgams in their mouth [10]. Keeping that in mind, let me tell you about some experiments that have been done at the University of Calgary Medical School in Canada [8,9]. These investigators drilled

cavities in the teeth of sheep. The teeth of sheep are very similar to those of humans but contact time is prolonged in herbivores [8]. They then prepared dental amalgam. Remember, dental amalgam in this country and in Canada, at the time it is prepared in the dentist's office, contains 40-60% metallic liquid mercury. These investigators added radioactive [²⁰³Hg] to dental amalgam at the time it was being prepared and used this radioactive amalgam to fill the dental cavities of a number of sheep. Within a relatively short period of time, the livers, kidneys and other tissues of these sheep become radioactive and the kidney, especially, contained significant amounts of radioactivity. In a subsequent study renal function was shown to be blocked [11]. The critics of these studies say that no normal human being gets 12 cavities filled in his mouth at one time. I, as a young boy, went to a dentist who put five in my mouth at one time. You all have your own nightmares, I am certain, about your own experiences at the dentist. Another criticism that has been made is that although these investigators showed that renal function was blocked, they did not continue the experiment to see whether renal function came back. Regardless, this controversy does exist in Europe and is beginning to increase in this country.

The Swedish government has recommended that amalgam fillings not be used in the future. In Germany, there have already been more than 1000 people tested with DMPS for mercury load. This has not necessarily been done with the approval of the manufacturer or the medical establishment. The reason I bring this all to your attention is that I know many of you are associated with poison control centers. Both DMPS and DMSA can be used in the treatment of mercury poisoning. In my opinion, DMPS is the better therapeutic agent for this purpose, since it mobilizes mercury at a faster rate than does DMSA [12].

Both DMSA and DMPS have been coming into this country illegally at the time this talk is being presented. Neither Johnson & Johnson, who make DMSA and are applying for a NDA, nor Heyl of Berlin, who makes DIMAVAL (DMPS), have had anything to do with the illegal importation of this material. I get a call at least once a month from individuals who say "I have a bottle of DMPS and a bottle of DMSA in front of me. I have mercury poisoning, What should I do? Which should I take?" I urge them to call their physician.

Let me say, it is for all these reasons that we have been asked to study DMPS, to see whether there is any scientific basis and evidence for its use in Germany as a diagnostic agent to determine amalgam mercury body loads.

We have started such a study, with our wonderful group of volunteer graduate students. These studies are in progress. I hope you will accept the data I shall present as a progress report. Please keep in mind the calcium sodium EDTA provocative or challenge test for lead poisoning and its problems [13].

Before the studies were performed in our laboratory, a dentist examined the mouths of these young men and gave them a number, called the amalgam score, based not only on the number of amalgam fillings, but also on the surface area of amalgams. The amalgam score was calculated as follows: A tooth was considered to be a five-sided cube (the sixth side invisible under the gums). If an amalgam surface had a diameter of 1 mm or less it was given a score of 1; a diameter above 1 and less than 2 mm, a score of 2; and a diameter of 3 mm or more a score of 3. Such a score was given to each amalgam surface on a tooth. The amalgam score is a summation of the score of all the amalgam surfaces on all the teeth in the subjects mouth. The dentist knew nothing about the urine levels of mercury. The person performing the mercury analyses in the lab knew nothing about the amalgam numbers. So these are sort of a blind test. Let me tell you some of the results, at this time, of these on going studies.

The subjects, after an overnight fast, were given 300 mg DMPS (DIMAVAL) po and their urine collected at the specified times. I shall show you the results from three of our volunteers. The first (Figure 6) is a person with the highest amalgam scores. The second (Figure 7) had a middle and the third had the lowest score (Figure 8). Figures 6, 7 and 8 also indicate the many fold increase in urinary mercury excretion after DMPS administration as compared to the predosing levels. The data, limited as it is at this time, clearly indicates that there is a relationship between the amalgam score and the amount of mercury excreted in the urine after the po administration of 300 mg DMPS. While others have shown there is a relationship between the number of amalgams and urinary mercury, many of those studies were performed at the very limit of the analytical methods used or they did not validate their analytical methods [10]. Our method has been validated and will be presented in a subsequent more detailed paper to be published elsewhere. Others have shown that DMPS increased urinary excretion of mercury but did not correlate this with amalgam surface area. Let me clearly state that the results of our experiments, limited as they are, should not be used to support either side of the controversy as to whether mercury amalgams are detrimental to ones health.

Our studies on this subject are continuing with a larger group of volunteers with and without dental amalgams. DMPS might be expected to increase the ease of measuring biological exposures to other toxic heavy metals and metalloids since its administration increases the urinary excretion of many of them [14-17]. Unlike the [CaNa.sub.2]EDTA challenge test which is now suspect as to its safety [13], DMPS does not cause a redistribution of Hg to the brain [12]. In addition, DMPS is more specific than [CaNa.sub.2]EDTA in that, at diagnostic doses, it would not be expected to increase in a clinically adverse manner the urinary excretion of essential metals such as copper and zinc [16].

The Zinc Chelate and Other New Forms of DMSA: Their Activities as Chelators of Platinum and Cadmium

Lastly, I would like to discuss with you our studies with newer analogs of DMSA which we tried to design so that they would enter cells where some metals are tightly bound. Cadmium, for example, is tightly bound to metallothionein, an intracellular polypeptide with many unusual properties. A chelating agent like DMSA, which is believed to have an extracellular, not an intracellular, distribution, has almost no effect on chronic cadmium intoxication. Why? One reason is that DMSA does not appear to be able to get into the cell where cadmium is bound very tightly to metallothionein.

To address the question of how to mobilize the more tenaciously held heavy metals like cadmium, we began thinking, quite sometime ago, about ways to modify the DMSA molecule. Dr. Mark Jones and his associates have also been interested in this problem [18,19]. His group found that as the member of a series of alkyl esters of DMSA increased in molecular weight, their toxicity increased [19]. This is to be expected since the less the charge on the carboxyl group in the molecules, the greater the expected lipophilicity of the molecule and thus the greater the chance of its entering the cell. We restricted our studies to synthesizing and studying the monomethyl ester (in which only one of the carboxyl groups of DMSA is esterified), the dimethyl ester of DMSA and the zinc chelate of the dimethyl ester of DMSA (Figure 9). The synthesis of the first and third compounds is not easy and had not been reported before. They were synthesized in a very clever manner by Mario Rivera, a graduate student working with Quintus Fernando, Professor of Chemistry at our university [20].

We became interested in these compounds after studies were performed in our lab to answer the question: do DMPS, DMSA or DMPA get into cells? It is not easy to prove rigorously that a drug enters a cell in vivo. In order to simplify our experimental parameters, we decided to use the bile to help answer this question. Our rationale was that if the drug appeared in the bile then it must have entered

liver cells first. In these experiments that were performed sometime ago in our lab [20,21], male rats were anesthetized, a cannula placed in the bile duct and the chelating agent administered iv. Of these dimercapto chelating agents (Figure 1), DMPA clearly appears in the bile (Figure 10), first in its unaltered form and then in its oxidized or altered form. As the amount of unaltered form decreased, that of the altered form increased. Whether this oxidation takes place in the liver or in the bile we do not know at the present time. But since we know that the parent compound is getting into the bile, it must be getting into the liver cells first. With DMPS, it is not a clear. A very small amount of unaltered DMPS appears in the bile but most of the DMPS is in an oxidized and therefore altered form (Figure 11). Either the DMPS is oxidized in the liver cells and altered DMPS only gets into the bile (with perhaps a small amount of enzymatic reduction there) or the DMPS is oxidized immediately on entering the bile. What is clear, however is that DMPS in some form is entering the liver cells. In all the experiments we have done, when DMSA is injected iv, we have never been able to detect it in the bile (Figure 11). Our methodology has been validated in many ways including our detecting very small amounts of DMSA in the bile after the iv injection of the dimethyl ester of DMSA but never after iv injection of DMSA. The toxicity of these compounds is related to whether or not they are able to get into cells (Table 2). DMSA which is the least toxic of these dimercapto chelating agents does not get into cells and has the highest [LD.sub.50]. DMPS which is able to enter cells to a limited extent (see also 22) is intermediate in its toxicity. DMPA, which readily enters the cells, is the most toxic.

TABLE 2

Compound	[LD.sub.50] LD50 (mmol/kg)	Determination 95% confidence interval	IP in Mice [23] Number of mice
BAL	1.48	1.11, 1.97	212
DMPA	0.82	0.80, 0.84	172
DMPS	6.53	5.49, 7.71	88
meso-DMSA	13.73	11.36, 15.22	164

Now let's go on with the zinc (Zn) chelate (Figure 9). In this compound two molecules of the dimethyl ester of DMSA are coordinated with a molecule of zinc. This compound was synthesized having in mind the severe calcium deficiency caused by EDTA during the early studies of this chelating agent. We reasoned that by giving this Zn chelate, it would enter the cell due to its decreased polarity and compete with metallothionein for firmly bound cadmium or firmly bound forms of cis-platinum in the cell, leaving zinc atoms in their place.

Cis-platinum is used in cancer chemotherapy. Its dose is limited by renal toxicity. Chemotherapists tell us that if they could give more cis-platinum without renal damage, they could increase the therapeutic benefits to the patient. We decided to see whether we could increase the biliary excretion of platinum by using this Zn chelate. An increase in biliary excretion might be expected to decrease renal excretion and therefore renal toxicity. In these experiments a relatively toxic dose of cis-platinum was given iv to male rats. Twenty-four h later the bile duct was cannulated and the Zn chelate of dimethylDMSA was given iv. The chelating agent increased the biliary excretion of platinum (Figure 12). An equimolar amount of the dimethyl ester of DMSA was about 50% as effective.

Similar results were found with cadmium. In rats given radioactive cadmium each day for three days, metallothionein synthesis was induced and was available for intracellular binding of cadmium. Administration of the Zn chelate produced a sharp increase in biliary excretion of cadmium (Figure 13). Many other questions pertaining to the DMSA Zn chelate remain to be answered. Further studies are in progress.

There are still many interesting questions to be answered about these most useful chelating agents. For example, are the chelate structures synthesized in the test tube by the organic chemists [20] the same as those chelate structures found in the urine after administering one of these chelating agents?

DMSA has been given to a relatively small number of patients. Will its administration to more people, as time goes on, result in more adverse effects being observed? One must keep in mind that DMPS has been used as Unithiol in the Soviet Union since the late 1950s and in Europe since the early 1980s.

The DMSA-cysteine mixed disulfide found in human urine after DMSA administration is not found when rodents are used. Are there more species specific surprises in store for us with these chelating agents?

Most of the pharmacokinetic and metabolism studies on DMSA and DMPS have been performed using normal healthy experimental animals and humans. Will the results of such studies be the same as those that will be done eventually in patients with heavy metal poisoning?

The experimental results that I have discussed with you are the results of interdisciplinary collaborative investigations by the Metals Groups of the University of Arizona, which include the research groups of Professor Quintus Fernando, Department of Chemistry, Professor Richard Dart, Department of Surgery, Professor Dean Carter, Department of Pharmacology and Toxicology, and my group in the University Department of Molecular and Cellular Biology.

Although I was asked to tell you about newer developments in our laboratory, I want to point out that other groups in the United States, such as those of Joseph Graziano at Columbia University, Julian Chisolm at the Johns Hopkins Medical College and Mark Jones at Vanderbilt University, have also studied DMSA or its analogs and have made numerous contributions to help understand the actions of DMSA and other important, orally useful chelating agents.

Let me summarize by saying that we have presented experimental evidence about the metabolites, pharmacokinetics and fate of DMSA when administered orally to humans. Second, I have attempted to make you aware of the dental amalgam controversy and a challenge test for body mercury using the chelating agent DMPS, marketed as DIMAVAL, in Europe. Finally, I introduced our studies using the Zn chelate of dimethyl DMSA.

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ADDENDUM

Since this paper was presented in September, 1990, some of the work that was in progress at that time has been completed and published. For a more up to date description of some of these studies the reader is directed to the following publications.

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