Arsenic Excretion after Treatment of Arsenic Poisoning with DMSA or DMPS in Mice

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Abstract—The effects of 2,3-dimercaptosuccinic acid (DMSA) and 2,3-dimercaptopropane-1-sulfonic acid, Na salt (DMPS) on arsenic excretion in arsenic poisoning were studied using ICR mice. One group of mice was given arsenic trioxide (5 mg As/kg, s.c.) and another two groups were given DMSA or DMPS (100 mg/kg, i.p.) immediately after administration of the arsenic (5 mg/kg, s.c.). Arsenic excretion in urine and feces was determined by atomic absorption spectrophotometry. Results obtained showed a marked arsenic excretion in the urine collected at the first 12 hr in the group treated with DMSA. Further remarkable arsenic excretion in the feces was seen in the group treated with DMPS, suggesting that arsenic might have been excreted in the bile.

In arsenic intoxication, dimercaprol (2,3-dimercaptopropanol, BAL) has been used as an antidote. However, its toxicity limits the amount of BAL that can be administered in therapeutic use. Aposhian (1) reviewed the recent advances of newly introduced dithiol compounds such as DMSA (2,3-dimercaptosuccinic acid, succimer) or DMPS (2,3-dimercaptopropane-1-sulfonic acid, Na salt) as promising heavy-metal antidotes. In our previous study (2), all mice which were given arsenic trioxide (LD100, 0.2 mmol/kg, p.o.) survived by the treatment with either one of these agents (0.4 mmol/kg, i.p.). DMPS also showed therapeutic effects against the acute poisoning with sodium arsenate and disodium monomethylarsonate, but it failed to show effectiveness in the sodium dimethylarsionate poisoning. DMSA improved the urinary excretion of arsenic, mercury, cadmium and lead in rats and mice (1). DMPS has been considered to have the same mechanism of metal excretion as DMSA (3, 4). However, there are few studies comparing these two antidotes. The present study concerns the different types of arsenic excretion between DMSA and DMPS.

Male ICR mice (23-30 g, 5 weeks of age, Shizuoka Laboratory Animal Center, Shizuoka) were used, and they were allowed free access to commercial diet (Oriental Yeast Co., Ltd, Tokyo) and tap water during the experiment. Ambient temperature was maintained between 24°-26°C. Arsenic trioxide (E. Merck, Darmstadt) was dissolved in an alkaline solution and after neutralizing, diluted with physiological saline. DMSA (Nakarai Chemicals, Ltd., Kyoto) was dissolved in 5% NaHC03 and DMPS (Sigma Chemical Co., St. Louis, MO) in physiological saline. All of these solutions were prepared immediately before use. Animals were divided into three groups of 12 mice, and as three mice were housed in the same metabolic cage during the experiment, each group consisted of four cages. One group was given a single dose of arsenic trioxide (5 mg, As/kg), subcutaneously. Another two groups were given DMSA or DMPS (100 mg/kg), intraperitoneally, immediately after administration of the arsenic (5 mg/kg, s.c.). Urine collections were made at 12 hr, 24 hr and 48 hr after the treatment. Feces were collected at 24 hr intervals over 2 days. Arsenic contents in the urine and feces were determined by atomic absorption spectrophotometry (5). Statistical significance was evaluated by Student’s t-test. Only P<0.05
was considered significant. Values were expressed as means or means±S.D.

Figure 1 shows excretion of arsenic in the urine and feces after a single dose of arsenic with and without DMSA or DMPS in mice.

In the first group given only arsenic trioxide (5 mg As/kg, s.c.), 66.7% of the administered dose was excreted in the urine 24 hr after the treatment, and 70.7% was seen as cumulative excretion after 48 hr. Arsenic in the feces was detected as 16.6% of the injected dose after 24 hr and 17.5% within 48 hr. Total arsenic eliminated from the urine and feces was 88.2±6.9% within 48 hr.

In the second group given arsenic (5 mg/kg, s.c.) and DMSA (100 mg/kg, i.p.), 80.6% and 81.3% of the dose were excreted in the urine 24 hr after the treatment and within 48 hr, respectively. Both of these values were not significantly different from the respective values of the first group. However, arsenic content in the urine, collected at the first 12 hr after the treatment, was found to be significant as compared to the corresponding value of the first group (37.8±5.5% for the first group and 76.3±6.7% for the second group). Arsenic in the feces in this group was similar to that in the first group. Total arsenic detected in the urine and feces in the second group was 94.6±10.7% of the dose within 48 hr.

In the third group given arsenic (5 mg/kg, s.c.) and DMPS (100 mg/kg, i.p.), a relatively small amount was detected in the urine, e.g., 33.5% of the dose after 24 hr and 34.4% after 48 hr. Both of these values were significantly low as compared to those at the same time of collection in the first and second groups. In contrast to the case in the former two groups, arsenic excretion in the feces exceeded that in the urine of this group, and the third group showed the following significant difference from those in the first and second groups: 61.7% after 24 hr in the third group as compared to 16.6% and 12.5% for the first and second groups, respectively. Total arsenic excretion in the urine and feces in the third group was 96.6±11.1% of the dose within 48 hr.

In summary, although total urinary and fecal excretion of arsenic within 48 hr was not significantly different among those three groups, DMSA improved the arsenic excretion in the urine in the early stage of intoxication and DMPS promoted the excretion through feces, the latter suggesting excretion of the chelated compound in the bile (biliary excretion of arsenic will be presented elsewhere).

It has been reported that DMPS improved the urinary excretion of mercury in rats (4, 5). In our previous study using rats (6), DMPS increased significantly the arsenic excretion in the feces as well as in the urine. Species difference of metal excretion should also be considered. Maiorino and Aposhian (7) pointed out that DMPS might readily enter hepatocytes, but DMSA might not. The results of the present experiment may be related to this difference.

References


