Comparison of the Effectiveness of 2,3-Dimercaptopropanol (BAL) and *meso*-2,3-Dimercaptosuccinic Acid (DMSA) as Protective Agents Against Mercuric Chloride-Induced Nephrotoxicity in Rats

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ABSTRACT

The effectiveness of 2,3-dimercaptopropanol (BAL) and *meso*-2,3-dimercaptosuccinic acid (DMSA) on HgCl₂-induced nephrotoxicity was studied in the rat. Seven groups of adult male rats were given a single sc toxic dose of HgCl₂ (0.68 mg/kg) followed by 0.9% saline (positive control group), BAL (15, 30, and 60 mg/kg) or DMSA (50, 100, and 200 mg/kg) administered ip at 0, 24, 48, and 72 h thereafter. Although the renal function of HgCl₂-exposed rats was slightly improved after BAL administration, Hg concentrations in the kidney were only reduced at 60 mg/kg. In addition, the protective effect of BAL was not dose-related. In contrast to BAL, DMSA was effective in increasing the urinary excretion of Hg and in reducing the renal Hg content. These results show that DMSA would be more effective than BAL in preventing or in protecting against inorganic Hg-induced nephrotoxicity.

Index Entries: Mercuric chloride; nephrotoxicity; 2,3-dimercaptopropanol (BAL); *meso*-2,3-dimercaptosuccinic acid (DMSA); rats.

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INTRODUCTION

Metal exposure can cause widespread glomerular, tubular, and other lesions in the kidney, a common target organ for toxic metals (1,2). The nephrotoxic effects of heavy metals, such as Cd, Cr, Pb, Hg, or U have been known for many years and are widely described (1-6). Among those metals, no other has been studied so thoroughly with respect to its action on the kidney than has Hg (7-12). It is well established that the nephropathological effects of Hg are largely dependent on the chemical form of exposure to this element (4). Thus, inorganic mercurials preferentially exert toxic effects on the third segment of the renal proximal tubule, whereas organomercurials exert toxic effects more extensively in all segments of the proximal tubules (4,7).

The major source of human Hg exposure is from various natural phenomena and from human activities (4). Although the majority of both biogenic and anthropogenic Hg emissions are in the form of elemental Hg (Hg⁰) to the air, once released to the atmosphere, Hg⁰ is oxidized to Hg²⁺, which can then complex with other ions, primarily Cl⁻, to form mercuric chloride, HgCl₂. Moreover, Hg deposits in water and soil are also oxidized to Hg²⁺ (13), which in tissues binds most likely to sulphydryl groups on proteins.

Regardless of the route of administration, HgCl₂ can induce acute tubular necrosis and acute renal failure in mammals, sometimes resulting in death (4). Two (and perhaps more) distinct mechanisms were recently suggested to be involved in the renal tubular uptake of inorganic Hg in vivo, the transport of organic anions, and the action of γ-glutamyltransferase (14). Since the kidneys accumulate more Hg²⁺ than any other organ, reducing the nephrotoxic effects of Hg is essential to diminishing the renal Hg accumulation.

The utility of chelating agents as antidotes for nephrotoxicity of a number of heavy metals has been widely investigated (15-19). With regard to Hg, in spite of the unavoidable side effects of 2,3-dimercaptopropanol (BAL), until recently this drug was used in the treatment of individuals suffering from Hg intoxication. However, in recent years, it has been shown that the water-soluble compounds meso-2,3-dimercaptosuccinic acid (DMSA) and sodium 2,3-dimercapto-1-propane sulfonate (DMPS) are less toxic and more effective chelating agents than the chemically analogous BAL (20,21). Although in recent studies both DMSA and DMPS were found to be very effective agents in reducing the renal burden of inorganic Hg in rats (22,23), the comparative antidotal efficacy of DMSA or DMPS in relation to BAL was not evaluated in those studies. In order to extend the information on the protective effects of chelation treatment on the nephrotoxic effects of inorganic Hg, in the present study, the comparative effectiveness of BAL and DMSA on mercuric chloride-induced nephrotoxicity was investigated in the rat.