

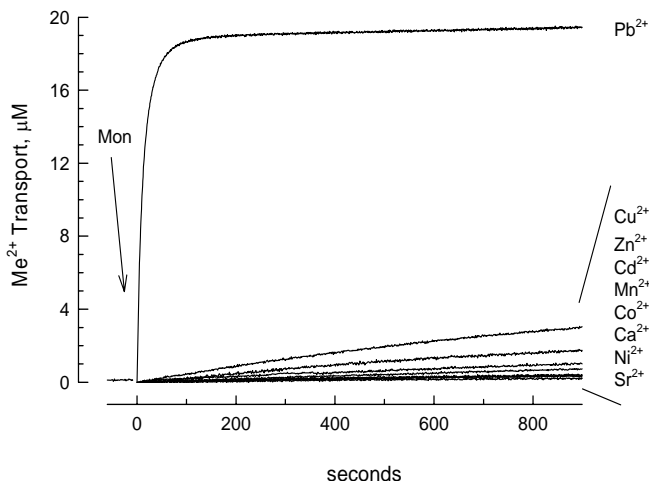
# Monensin Improves the Effectiveness of *meso*-Dimercaptosuccinate when used in the Treatment of Pb Intoxication

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**ABSTRACT.** Among divalent cations, the carboxylic acid ionophore monensin shows high activity and selectivity for the transport of  $Pb^{2+}$  across phospholipid bilayer membranes (Fig. 1).

*Figure 1. Relative efficiency of monensin catalyzed divalent cation transport into phospholipid vesicles. The vesicles were loaded with a chelating-indicator to allow monitoring of the transport process by dual wavelength spectroscopy. For experimental details see S. A. Hamidinia et.al. (2002) J. Biol. Chem. 277, 38111-38120.*



When co-administered to rats (100 ppm in feed) that were receiving *meso*-dimercaptosuccinate (DMSA) for treatment of Pb intoxication (three week treatment periods), monensin significantly increased the amount of Pb removed from femur, brain, and heart. It showed a tendency to increase Pb removal from liver and kidney, but had no effect of this type in skeletal muscle. Tissue levels of several physiological (Ca, Co, Cu, Fe, Mg, Mn, Mo, Zn) and non-physiological (As, Cr, Cd, Ni, Sr) elements were also determined following the application of these compounds. Among the physiological elements a number of significant changes were seen; including both rising and falling values. The size of these changes was typically around 20%, compared to control values, with the largest examples seen in femur. These changes often tended to reverse those of similar size that had occurred during Pb administration. Among the non-physiological elements, which were present only in trace amounts, the significant changes were smaller in number but larger in size. None of these changes appear likely to be significant in terms of toxicity, and there were no signs of overt toxicity under any of the conditions employed. Monensin may act by co-transporting  $Pb^{2+}$  and  $OH^-$  ions out of cells, in exchange for external  $Na^+$  ions (Fig. 2).

*Figure 2. Proposed mechanism for monensin catalyzed  $Pb^{2+}$  depletion from cells.*

The net effect would be to shuttle intracellular  $Pb^{2+}$  to extracellular DMSA, thereby enhancing its effectiveness. Thus, monensin may be useful for the treatment on Pb intoxication when applied in combination with a hydrophilic  $Pb^{2+}$  chelator.

