

HEALTH AND HUMAN SCIENCES

Manganese-Induced Parkinsonism: Relationship to Manganese Accumulation in Bone

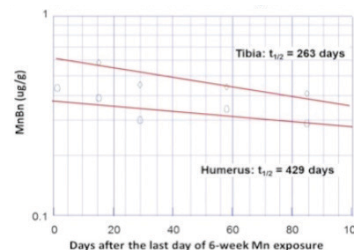
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Exposure to the toxic metal manganese (Mn) can cause a neurodegenerative condition known as manganism, with signs and symptoms similar to, but distinguishable from, idiopathic Parkinson’s disease. Mn overexposure is predominantly observed as a result of welding, smelting, and pesticide exposure, as well as among drug abusers. Mn accumulates in the osseous tissues of the body due to its chemical interaction with calcium. Mn stored in bone may serve as an internal reservoir that continuously poisons the brain by releasing Mn into the blood. At present, answers to questions as to how long Mn may accumulate in bone and to which fraction of bone structures Mn is bound remain elusive. Understanding these critical issues is of great importance for clinical assessment of Mn body burden and for development of therapeutic intervention. The aims of this work were twofold: to determine the biological half-life ($T_{1/2}$) of Mn in bone and to assess substructural location of Mn in bone.

In a subchronic Mn exposure animal model, rats received oral gavage of 50 mg Mn/kg (as MnCl₂) or saline (as controls) over 6 weeks. After the last dose, rats were sacrificed at 24 hours, 2 weeks, 1, 2, or 3 months; bone samples (tibia and humerus) and brain samples were collected and weighed. Samples were digested in concentrated nitric acid in a high-pressure microwave digester. Atomic absorption spectrophotometric analyses were performed to determine the concentration of Mn in each tissue. Average values were plotted over time; the elimination rate constants (Ke) were calculated from the slopes of the linear regressions of the terminal elimination phases. Ke values were then used to estimate the $T_{1/2}$ of Mn in bone. The data shows that Mn exposure caused a significant accumulation of the metal in bone tissues (2-3 fold, $p < 0.05$, $n = 4-6$). Linear regression

analysis revealed that the $T_{1/2}$ ’s of Mn in tibia and humerus bone were 263 and 429 days, respectively. The $T_{1/2}$ of Mn in striatum was estimated about 117 days from the same experiment. By comparison, the earlier work by this group shows that the $T_{1/2}$ of Mn in rat plasma is about 1.8 hours. The current study also found that the Mn levels in bone and brain were well correlated, suggesting that a slow release of Mn deposited in bone over a long period of time may contribute to Mn accumulation in brain and the ensuing Parkinsonian disorders. Since 16.7 rat days are estimated to be equivalent to one human year, I predict that Mn $T_{1/2}$ ’s in human bone could reach between 15–26 years. Such a long half-life and high concentrations of Mn in bone suggest that bone Mn is a reliable biomarker for Mn exposure assessment. The findings in this study also call for engineering design of noninvasive new technology for quantifying Mn in bone. Furthermore, my recent findings on substructural bone analysis indicate that Mn accumulation appeared to be greater in trabecular bone than in cortical bone tissue. Studies to confirm this compartmental distribution of Mn in bone are currently in progress.

Research advisor Wei Zheng and student mentor Stefanie O’Neal write, “Jones’s study on Mn accumulation in bone demonstrates that toxic exposure to Mn causes its deposition primarily in human bone tissue for decades. As Mn is known to cause Parkinson-type neurodegeneration, this study has built the theoretical foundation on which to develop the means for health/risk assessment of Mn toxicity.”



Half-lives of Mn in rat bone following subchronic Mn exposure of 6 weeks. Tibia $T_{1/2}$ = 263 days. Humerus $T_{1/2}$ = 429 days.

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