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Manganese accumulation in bone following chronic exposure in rats: Steady-state concentration and half-life in bone

Stefanie L. O'Neal, Lan Hong, Sherleen Fu, Wendy Jiang, Alexander Jones, Linda H. Nie, Wei Zheng *

School of Health Sciences, Purdue University, West Lafayette, IN 47907, USA

HIGHLIGHTS

- We examine the steady-state level and half-life of Mn in bone after oral exposure.
- Average $t_{1/2}$ of Mn in bone approximates 143 days in rats and 8.5 years in humans.
- Mn concentrations in bone correlate with Mn levels in brain tissues and CSF.
- We conclude that bone Mn is potentially a reliable biomarker for risk assessment.

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ABSTRACT

Literature data indicate that bone is a major storage organ for manganese (Mn), accounting for 43% of total body Mn. However, the kinetic nature of Mn in bone, especially the half-life ($t_{1/2}$), remained unknown. This study was designed to understand the time-dependence of Mn distribution in rat bone after chronic oral exposure. Adult male rats received 50 mg Mn/kg (as $MnCl_2$) by oral gavage, 5 days per week, for up to 10 weeks. Animals were sacrificed every 2 weeks during Mn administration for the uptake study, and on day 1, week 2, 4, 8, or 12 after the cessation at 6-week Mn exposure for the $t_{1/2}$ study. Mn concentrations in bone (MnBn) were determined by AAS analysis. By the end of 6-week's treatment, MnBn appeared to reach the steady state (T_{ss}) level, about 2–3.2 fold higher than MnBn at day 0. Kinetic calculation revealed $t_{1/2}$s of Mn in femur, tibia, and humerus bone of 77 ($r = 0.978$), 263 ($r = 0.988$), and 429 ($r = 0.994$) days, respectively; the average $t_{1/2}$ in rat skeleton was about 143 days, equivalent to 8.5 years in human bone. Moreover, MnBn were correlated with Mn levels in striatum, hippocampus, and CSF. These data support MnBn to be a useful biomarker of Mn exposure.

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1. Introduction

Occupational exposure to manganese (Mn), such as in mining, smelting, welding or dry-cell battery production, has been associated with a neurodegenerative Parkinsonian disorder clinically called manganism (Barbeau et al., 1976; Chandra et al., 1981; Crossgrove and Zheng, 2004; Jiang et al., 2006). Environmental exposure to this toxic metal has also been linked to the consumption of Mn-containing pesticides and contamination in drinking water and food (Bouchard et al., 2011). Addition of Mn to gasoline as the anti-knocking reagent, methylcyclopentadienyl Mn tricarbonyl (MMT) further raises concerns about health risks associated with a potential increase in environmental levels of Mn (Butcher et al., 1999; Sierra et al., 1995). Recently, increasing numbers of cases of Mn-induced Parkinsonism have been observed among drug addicts using ephedrone (Sikk et al., 2011). It is because of rising public health concerns that a thorough understanding of Mn neurotoxicity, including its distribution in the body and mechanism of action, is well justified.

Patients suffering from manganism have signs and symptoms closely resembling, but not identical to, Parkinson's disease (PD) (Aschner et al., 2007; Jiang et al., 2006; Racette et al., 2012). Recent data also show that Mn may play a role in PD etiology (DeWitt et al.,

Abbreviations: Mn, manganese; MnBn, Mn concentration in bone; MnM, Mn concentration in muscle; CSF, cerebrospinal fluid; BBB, blood–brain barrier; BCB, blood–cerebrospinal fluid barrier; T_{ss}, steady state concentration; $t_{1/2}$, half life.

* Corresponding author at: School of Health Science, Purdue University, 550 Stadium Mall Drive, CIVL 1173, USA. Tel.: +1 765 496 6447; fax: +1 765 496 1377.
E-mail address: wzheng@purdue.edu (W. Zheng).

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2013; Lucchini et al., 2007). Since clinically manifested Mn neurotoxicity is usually progressive and irreversible, early diagnosis becomes critical to treatment and prevention of Mn intoxication. Historically, searches for biomarkers of Mn exposure and health risk have focused on Mn concentrations in blood, urine, and/or nail. These biomarkers, however, are of limited use for exposure assessment in that primarily intracellular accumulation of Mn renders blood, urine, or nail Mn levels inaccurate in reflecting the true body burden of Mn (Apostoli et al., 2000 Zheng and Monnot, 2012). For example, in group comparisons among active workers, blood Mn has some utility for distinguishing exposed from unexposed subjects; yet a large variability in mean values renders it insensitive for discriminating one individual from the rest of the study population. Human studies using magnetic resonance imaging (MRI), in combination with non-invasive assessment of γ-aminobutyric acid (GABA) by MR spectroscopy (MRS), have provided evidence of Mn exposure in patients devoid of clinical symptoms of Mn intoxication (Dydak et al., 2011; Jiang et al., 2007). These methods, however, do not provide an adequate estimation of Mn body burden in a long-term, low-dose Mn exposure scenario (Zheng and Monnot, 2012). Thus, to date, a reliable biomarker to accurately reflect Mn exposure or body burden remains unavailable.

Data in literature suggest that, at normal physiological conditions, Mn accumulates extensively in human bone tissues (Pejovic-Milic et al., 2009; Schroeder et al., 1966; Zaichick et al., 2011). Schroeder et al. (1966) observed an average concentration of 2 mg/kg of Mn in bone ash, which gives rise to about 32.5% of body Mn in bone, according to our recent calculation (Liu et al., 2013). The International Commission on Radiological Protection (ICRP) has reported approximately 40% of body Mn accumulates in bone (ICRP, 1972). Information from animal studies of Mn accumulation in bone can be found in literature, albeit is very limited (Dorman et al., 2005 Seaborn and Nielsen, 2002). Using a physiologically-based pharmacokinetic modeling approach, Andersen et al. (1999) reported that Mn stored in bone tissues contributed to over 40% of body Mn; the estimate is closer to the aforementioned human data. Studies by Furchner et al. (1966) using radioactive ^{54}Mn administered orally to rats at a normal physiological dose have found that the radioisotope in bone had a half-life of more than 50 days, which was much longer than the ^{54}Mn half-life in other rat tissues. Another study by Newland et al. (1987) in primates using ^{54}Mn reported that Mn had a relatively long half-life of about 220 days in the whole head after inhalation exposure. In the same study, the researchers found that the half-life of ^{54}Mn in brain tissues from the same animals was much shorter; hence they ascribed a long half-life of ^{54}Mn in the head to ^{54}Mn present in the skull or to replenishment from other depots (Newland et al., 1987). These data have clearly established that bone is one of the major organs for long-term storage of Mn in the body. Thus, a reliable assessment of Mn health benefits or risks should take into account the extensive Mn deposition in bone. However, knowledge on the rate of Mn accumulation in human or animal bone, and the pertinent biological half-life of Mn in bone was incomplete.

Recent advances in neutron activation-based detection technology has made it possible to develop a transportable neutron activation analysis (NAA) system for quantifying MnBn (Liu et al., 2013). This highly innovative technique uses a portable deuterium–deuterium (DD) neutron generator (as the neutron source) to detect Mn in bone, non-invasively and in real time, in human subjects. To support this technical innovation, there was a need to understand the toxicokinetics of Mn in bone under a long-term, low-dose exposure condition. The current study is part of a larger research effort at Purdue University (Liu et al., 2013) to use MnBn as a reliable biomarker for the noninvasive assessment of Mn body burden in humans.

The purposes of the current study were to (1) characterize the time-dependent accumulation of Mn in rat bone following chronic oral administration of Mn to animals; (2) determine the elimination $t_{1/2}$ of Mn in bone tissues; (3) investigate if bone samples collected from different body parts had similar or different kinetic characteristics; and (4) seek the correlations between MnBn and Mn concentrations in select brain regions known to be targets of Mn neurotoxicity. Understanding the time-dependent changes of tissue distribution of Mn within bone, central nervous system (CNS), and other tissues will help discover a novel biomarker suitable for the assessment of Mn exposure in humans.

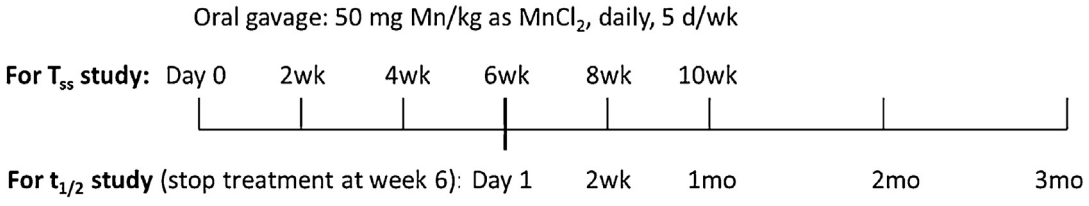
2. Materials and methods

2.1. Chemicals

Chemical reagents were purchased from the following sources: Mn chloride tetrahydrate ($MnCl_2{\cdot}4H_2O$) from Fisher Scientific (Pittsburgh, PA); Mn and Cu standard solutions were from SCP Science (Champlain, NY); ketamine from Fort Dodge (Fort Dodge, IA); and xylazine from Vedco (St. Joseph, MO). All reagents were analytical grade, HPLC grade, or the best available pharmaceutical grade.

2.2. Experimental design

The overall experimental design is illustrated below:



Phase 1 studies were designed to determine the time course of Mn accumulation in bone. Rats received daily administration of 50 mg Mn/kg as $MnCl_2$ by oral gavage, 5 days per week for the period of time specified in the above illustration. In this phase, dose administration lasted up to 10 weeks with cohorts of animals sacrificed every 2 weeks to determine the steady state Mn concentrations (T_{ss}) in bone following oral exposure.

Phase 2 studies were designed to determine the elimination $t_{1/2}$ of Mn from bone tissues. The results from Phase 1 suggest a T_{ss} was reached by 6 weeks of continuous Mn exposure. After the last dose of the week-6 dose administration, animals were sacrificed at 24 h, 2 weeks, 1–3 months to determine $t_{1/2}$ of MnBn.

2.3. Animals and Mn administration

Male Sprague Dawley rats were purchased from Harlan Laboratories, Inc. (Indianapolis, IN). Upon arrival, animals were housed in a temperature-controlled, 12-h light/dark cycle room and allowed to acclimate for 1 week prior to experimentation. At

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