

BIOMARKERS FOR MANGANESE EXPOSURE AMONG WELDERS AND CARDIOVASCULAR TOXICITIES

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ABSTRACT

The objective of present day study was to assess relationship between biomarkers of manganese and neuropsychological effects. Manganese (Mn) is an essential element for many biological functions in human beings. However, over exposure to manganese can causes health problems especially neurotoxicity. Mn accumulates in the brain regions and it cause central nervous system (CNS) abnormality and neuropsychiatric disorder. The respiratory system is the most important way of Mn absorption for workers in Mn related industries. Welders are exposed to relatively high concentrations of manganese and while the neurotoxicity of manganese is well documented, Few studies have investigated the cardiac effects of occupational manganese exposures. By examining electrograms (ECG) and heart rate variability (HRV), the cardiac conditions among the welders are clearly determined. Blood, nails, hairs were taken as biomarker. But the most suitable biomarker is hair because of its slow growth rates, less influenced by short term variability of manganese exposure levels.

Keywords: *Manganese, Occupational exposure, Ecocardiogram, Biomarkers, Neuropsychiatric disorder*

INTRODUCTION

Welders are exposed to relatively high concentration of manganese during the process of welding. Neurotoxicity of manganese exposure and the neurological health effects among welders are well documented (Elingsen, Heltland & Thomassen, 2003). The presentation is a review on biomarkers of manganese exposure detected in biological materials like blood, hair, nail and maternal-infant biomarkers.

MANGANESE

Manganese is an essential element for many biological functions in life forms including man. It is observed as Mn²⁺ ion. It function as activator of a number of enzymes like oxidases, peroxidases, dehydrogenase, kinases and decarboxylases, maintain lamellar structure of chloroplast, essential for photolysis of water and evolution of oxygen. Deficiencies may cause necrosis, leaves show premature fall or do not develop at all, flowers are often sterile.

Welders and manganese exposure

Welders are exposed to manganese during the process of welding when molten metal from mild or stainless steel or from manganese containing electrodes or wire is volatilised (Hassani *et al.*, 2012 and Cowan *et al.*, 2009). Volatilised welding fumes are small in size, mainly spherical particles ranging from 50 to 300 nm in

diameter. These small particles have the ability to reach deep into the alveolar region of the lungs where they can initiate health effects.

What is manganism

Toxicological studies suggested that the small particles of manganese may be transported via olfactory nerves where they can initiate a cascade for central nervous system effects. Inhaled manganese may induce a Parkinson like neurodegenerative disease called manganism.

Neurological symptoms are:

1. Reduced response speed
2. Irritability
3. Mood changes
4. Compulsive behaviour

Biomarker

Biomarker is a measurable indicator of severity or presence of some physiologically altered or diseased state. It can be used as indicator of particular disease or some physiological state of an organism. Biomarkers can be specific cell, molecule, gene product, enzymes or hormone. Numerous biological media including whole blood, serum, urine, nails, toenails, hair and maternal-infant biomarkers of prenatal exposure to manganese have been tested. But the simplest biomarkers are as follows.

Hair as a biomarker

Hair manganese as a biomarker has the advantage over blood and urine that is less influenced by short-term variability of Mn exposure levels because of its slow growth rate. Hair manganese levels may reflect environmental Mn exposure over the period of hair growth (e.g. Month) better than other commonly used exposure biomarkers such as urine or blood (Smith *et al.*, 2007)

Maternal-infant biomarkers

Because manganese is able to pass the placenta, infant among exposed populations may be exposed at considerable level in utero. It is possible to evaluate infant toe, nails, hair and cord blood as biomarkers of parental exposures to manganese and relationship between maternal and infant manganese concentration can be determined (Rodrigues *et al.*, 2015).

Cardiovascular toxicities in exposed workers

In a study from a smelting manufacturer producing Mn, the geometric mean concentration of airborne Mn in the working environment was 0.07 mg/m³. It was found that heart rates were significantly faster and the P-R intervals were significantly shorter in female smelting workers than those of female control. QRS waves and T waves are also wider and more elevated, respectively in both female and male smelting workers than in control (He, *et al.*, 2002). When the geometric mean concentrations of airborne MnO₂ in the working air were between 0.05 and 2.15 mg/m³, the incidences of abnormal ECG in workers were markedly increased as compared with the control subjects.

Possible Mechanisms of Mn-Induced Cardiovascular Toxicities

Altered Autonomic Nervous Function

The cardiovascular functions are precisely regulated by the autonomic nervous system, a minor alteration in the autonomic function could lead to profound detrimental outcomes in both cardiac and vascular performance. Mn-exposed workers show a disturbed autonomic nervous function (He *et al.*, 2002; Magari *et al.*, 2002). This disturbance could lead to the change of cardiac rhythm and blood pressure seen in clinics. More detailed studies must be done in order to verify Mn's effect on autonomic nervous function.

Reduced DA, 5-HT, Disturbed Cholinesterase Synthesis, and Reduced Superoxide Dismutase Activity

Dopamine (DA) and serotonin (5-HT) are important neurotransmitters involved in the regulation of cardiovascular functions. Dopamine, by acting on the D1 receptor, causes vasodilatation, whereas 5-HT causes vasoconstriction via binding to 5-HT₂ receptors on blood vessels. It is reported that Mn²⁺ reduced cellular dopamine levels more than Mn³⁺, especially at the highest exposures (50% reduced at 200 μM Mn²⁺) in PC12 cells. In contrast, Mn³⁺ produced a >70% reduction in cellular 5-HT at all exposure levels as compared with Mn²⁺. The differential effects of Mn²⁺ vs Mn³⁺ exposures on cellular toxicity cannot be attributed simply to the different cellular levels of Mn. Thus, the oxidation state of Mn exposures may play an important role in mediating Mn cytotoxicity. Mn has also been found to disturb the synthesis of cholinesterase, which causes accumulation of acetylcholine (ACh). The disturbed autonomic nervous function can lead to the altered rhythm of the heart as well as of the blood pressure (Reaney *et al.*, 2005).

The superoxide dismutase (SOD), which requires Mn for its activity, plays a significant role in vascular contractility. A diminished SOD activity and an increased superoxide anion level have been linked to oxidative stress-induced vasodilatation (Sun *et al.*, 2003). However, the study conducted in a rat model has shown that Mn exposure did not cause any significant change in SOD activity in the heart as compared with controls (Franco *et al.*, 2002).

Vascular effect on manganese exposure

Among workers who were exposed to Mn dust the mean diastolic pressure of these workers was significantly lower than that of control subjects, and the incidence of diastolic hypotension in these Mn-exposed workers was significantly higher than that in controls. The diastolic pressure among Mn-exposed workers tended to decline with the increase of exposed time and age. It was also found that the incidence of diastolic hypotension was significantly higher in the age group of 20–30 years than in other age groups, and significantly higher in female workers exposed to Mn than in their male counterparts. It appeared in such studies that young and female workers are more susceptible to Mn-induced vascular dilation effect. Mn

exposure causes vasodilatation, leading to a decline in diastolic pressure (Su *et al.*, 1998). QRS waves were significantly widened, their T waves elevated, and their mean diastolic blood pressure significantly reduced in comparison with control subjects. Similarly, the workers with the highest level of exposure to Mn had the lowest systolic blood pressure.

Damage to myocardial mitochondria

Within the cell compartment, the mitochondrion is the primary subcellular organelle to accumulate Mn. Once inside the mitochondria, Mn can interact with enzymes that are involved in the respiratory chain. Alteration in mitochondrial energy production can compromise the cardiac function. Mn has been shown to inhibit the activity of mitochondrial aconitase, whose function is critical to electron transfer during the production of ATP. Mn may cause a decrease in cytochrome oxidase and succinate dehydrogenase activity in the mitochondrial respiratory chain, a disturbance in oxidative phosphorylation, and a decline in oxygen utilization rate, all of which may induce structural and functional alterations of other subcellular organelles and components.

Effects neurotransmitter regulation

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Blockage of Ca²⁺ channel

In the heart, Mn appears to block the Ca channel so that the excitation phase is separated from the contraction phase in the myocardium, which ultimately leads to a decrease in the contractility of the heart. The Ca slow channel possesses a binding site for substrate Ca. Mn appears to have a higher affinity than Ca for the acceptor-combine site in the Ca slow channel, which explains the inhibitory effect of Mn on the Ca channel. In blood

vessels, Mn may also exert similar inhibitor action by blocking the coupling process between excitation and contraction of the vascular smooth muscle. This could contribute to Mn-induced hypotension.

CONCLUSION

Mn exposure significantly alters cardiovascular function despite the lack of epidemiological data on cardiovascular morbidity and mortality on Mn workers in the current literature. Mn exposure produces abnormal ECG and inhibits myocardial contraction. With regard to vascular function, Mn exposure dilates the blood vessel and induces hypotension. Mn-induced cardiovascular toxicities appear to be associated with chronic exposure in humans. However, a well defined clinical characterization of such Mn cardiovascular toxicity is still lacking.

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