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A systematic study of the disposition and metabolism of mercury species in mice after exposure to low levels of thimerosal (ethylmercury)☆

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ABSTRACT

Thimerosal (TM) is an ethylmercury (etHg)-containing preservative used in some vaccines despite very limited knowledge on the kinetics and direct interaction/effects in mammals' tissues after exposure. Thus, this study aimed to evaluate the kinetics of Hg species in mice in a time course analysis after intramuscular injection of TM, by estimating Hg half-lives in blood and tissues. Mice were exposed to one single intramuscular dose of 20 μg of Hg as TM. Blood, brain, heart, kidney and liver were collected at 0.5 hour (h), 1 h, 8 h, 16 h, 144 h, 720 h and 1980 h after TM exposure ($n=4$). Hg species in animal tissues were identified and quantified by speciation analysis *via* liquid chromatography hyphenated with inductively coupled mass spectrometry (LC–ICP-MS). It was found that the transport of etHg from muscle to tissues and its conversion to inorganic Hg (inoHg) occur rapidly. Moreover, the conversion extent is modulated in part by the partitioning between EtHg in plasma and in whole blood, since etHg is rapidly converted in red cells but not in a plasma compartment. Furthermore, the dealkylation mechanism in red cells appears to be mediated by the Fenton reaction (hydroxyl radical formation). Interestingly, after 0.5 h of TM exposure, the highest levels of both etHg and inoHg were found in kidneys (accounting for more than 70% of the total Hg in the animal body), whereas the brain contributed least to the Hg body burden (accounts for $<1.0\%$ of total body Hg). Thirty days after TM exposure, most Hg had been excreted while the liver presented the majority of the remaining Hg. Estimated half-lives (in days) were 8.8 for blood, 10.7 for brain, 7.8 for heart, 7.7 for liver and 45.2 for kidney. Taken together, our findings demonstrated that TM (etHg) kinetics more closely approximates Hg^{2+} than methylmercury (meHg) while the kidney must be considered a potential target for etHg toxicity.

1. Introduction

Thimerosal (TM), which contains ethylmercury (etHg), has been widely used as a preservative in a number of drug products, including vaccines, to help prevent life-threatening contamination with microbes (Tan and Parkin, 2000). However, the potential neurotoxic effects of organomercurial compounds, even at low exposures (Lebel et al., 1998; Berman et al., 2008; Delong, 2011; Bose et al., 2012; Petroni et al., 2012; Ida-Eto et al., 2013), have provoked concerns about the use of thimerosal in vaccines and other products (Clements et al., 2000; Ball et al., 2001).

The toxic properties of Hg compounds are directly related to the chemical form of the element. In general, exposure to organic forms of Hg is associated with nervous system damage, while inorganic forms are closely connected to renal damage (Clarkson and Magos, 2006). However, the toxicokinetics and potential toxic properties of TM (etHg) are mostly unknown (WHO, 2012).

Due to the lack of information about the behavior of TM in the mammalian body, the initial risk assessments for etHg were based on studies of oral methylmercury (meHg) toxicity. However, recent

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