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Dose–response study of thimerosal-induced murine systemic autoimmunity

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Abstract

The organic compound ethylmercurithiosalicylate (thimerosal), which is primarily present in the tissues as ethylmercury, has caused illness and several deaths due to erroneous handling when used as a disinfectant or as a preservative in medical preparations. Lately, possible health effects of thimerosal in childhood vaccines have been much discussed. Thimerosal is a well-known sensitizing agent, although usually of no clinical relevance. In rare cases, thimerosal has caused systemic immune reactions including acrodynia. We have studied if thimerosal might induce the systemic autoimmune condition observed in genetically susceptible mice after exposure to inorganic mercury.

A.SW mice were exposed to 1.25–40 mg thimerosal/l drinking water for 70 days. Antinucleolar antibodies, targeting the 34-kDa protein fibrillarin, developed in a dose-related pattern and first appeared after 10 days in the two highest dose groups. The lowest observed adverse effect level (LOAEL) for antifibrillarin antibodies was 2.5 mg thimerosal/l, corresponding to an absorbed dose of 147 μg Hg/kg bw and a concentration of 21 and 1.9 μg Hg/g in the kidney and lymph nodes, respectively. The same LOAEL was found for tissue immune-complex deposits. The total serum concentration of IgE, IgG1, and IgG2a showed a significant dose-related increase in thimerosal-treated mice, with a LOAEL of 5 mg thimerosal/l for IgG1 and IgE, and 20 mg thimerosal/l for IgG2a. The polyclonal B-cell activation showed a significant dose–response relationship with a LOAEL of 10 mg thimerosal/l. Therefore, thimerosal induces in genetically susceptible mice a systemic autoimmune syndrome very similar to that seen after treatment with inorganic mercury, although a higher absorbed dose of Hg is needed using thimerosal. The autoimmune syndrome induced by thimerosal is different from the weaker and more restricted autoimmune reaction observed after treatment with an equipotent dose of methylmercury.

Keywords: Thimerosal; Ethylmercury; Mice; Autoimmunity

Introduction

In a recent review Clarkson (2002) described thimerosal in vaccines as one of three modern faces of mercury, the two other being methylmercury in fish and mercury vapor from dental amalgam fillings. Thimerosal is an organic, alkylmercury compound in which an organic radical, ethylmercury, is bound to the sulfur atom of the thiol group of salicylic acid. The type of anion attached to ethylmercury affects neither the distribution of mercury in the body nor the toxicity (Suzuki et al., 1973; Ulfvarson, 1962), while the organic radical has a strong impact on both (Magos, 2003). Ethylmercury and its decomposition product, Hg^{2+}, rapidly accumulate in the tissues (Magos, 2001).

Ethylmercury has been frequently used since it was first synthesized in the 19th century. When used as a seed disinfectant in developing countries, it caused several outbreaks of poisoning with neurological symptoms and signs similar to those of methylmercury intoxication (Clarkson, 2002). Such manifestations have also been recorded after occupational exposure and after use as a wound disinfectant and a preservative in medical preparations (Magos, 2001). A number of severe intoxications and deaths have occurred with the use of erroneous concentrations of thimerosal in medical preparations during the last 30 years (Axton, 1972; Suzuki et al., 1973).

Since the 1930s, thimerosal has been used world-wide as a preservative in vaccines, a use that was approved as late as 1976 by the U.S. Food and Drug Administration

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