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Thimerosal induces micronuclei in the cytochalasin B block micronucleus test with human lymphocytes

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Abstract Thimerosal is a widely used preservative in health care products, especially in vaccines. Due to possible adverse health effects, investigations on its metabolism and toxicity are urgently needed. An in vivo study on chronic toxicity of thimerosal in rats was inconclusive and reports on genotoxic effects in various in vitro systems were contradictory. Therefore, we reinvestigated thimerosal in the cytochalasin B block micronucleus test. Glutathione S-transferases were proposed to be involved in the detoxification of thimerosal or its decomposition products. Since the outcome of genotoxicity studies can be dependent on the metabolic competence of the cells used, we were additionally interested whether polymorphisms of glutathione S-transferases (GSTM1, GSTT1, or GSTP1) may influence the results of the micronucleus test with primary human lymphocytes. Blood samples of six healthy donors of different glutathione S-transferase genotypes were included in the study. At least two independent experiments were performed for each blood donor. Significant induction of micronuclei was seen at concentrations between 0.05–0.5 µg/ml in 14 out of 16 experiments. Thus, genotoxic effects were seen even at concentrations which can occur at the injection site. Toxicity and toxicity-related elevation of micronuclei was seen at and above 0.6 µg/ml thimerosal. Marked individual and intraindividual variations in the in vitro response to thimerosal among the different blood donors occurred. However, there was no association observed with any of the glutathione S-transferase polymorphism investigated. In conclusion, thimerosal is genotoxic in the cytochalasin B block micronucleus test with human

lymphocytes. These data raise some concern on the widespread use of thimerosal.

Keywords Thimerosal · Cytokinesis-block micronucleus assay · Glutathione S-transferase

Introduction

Thimerosal {sodium ethyl[2-mercaptobenzoato(2-)-O, S]mercurate(1-), CAS 54-64-8}, is used as a preservative in medical products, especially in hepatitis B vaccines. The discussion on toxic effects of thimerosal is mainly focussed on its mercury content (Ball et al. 2001). In addition, the substance is known to be a contact sensitizer (Schnuch et al. 1998). Possible carcinogenic effects were investigated in one study on the chronic toxicity of thimerosal in Fischer 344 rats (Mason et al. 1971). However, this study does not meet the requirements of the current guidelines and does not rule out a possible carcinogenic effect of thimerosal.

In addition, there were reports on genotoxic effects of thimerosal in vivo. A weak but significant increase in micronuclei and chromosome aberrations was seen in male Swiss CD-1 mice at doses between 10 and 20 mg/kg (Marrazzini et al. 1994); another study using male and female (102/E1×C3H/E1)F₁ mice and Swiss albino mice reported negative results (Adler et al. 1991).

Reports on genotoxic effects in in vitro systems were contradictory. According to the acceptance criteria outlined by the GUM (German Section of the European Environmental Mutagen Society) working group on the evaluation of published data of the in vitro micronucleus test, only two valid reports on the effects of thimerosal in this test system were available (Miller et al. 1998). A weak but significant induction of micronuclei was found at concentrations between 0.01 and 0.16 µg/ml in two out of three experiments with human lymphocytes from two donors (Migliore and Nieri 1991). A significant elevation of micronuclei in V79 cells was induced by

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