Review on the Toxicity of Ethylmercury, Including its Presence as a Preservative in Biological and Pharmaceutical Products

L. Magos*
TNO BIBRA International Ltd, Woodmansterne Rd, Carshalton, Surrey SM5 4DS, UK

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INTRODUCTION

The interest in ethylmercury has been raised lately by a letter sent to The Lancet suggesting that ethylmercurythiosalicylate preservative (product names: Thimerosal, Thiomersal, Merthiolate) in hepatitis B immunoglobulin (HBIG) caused severe ethylmercury intoxication. Most likely as a reverberation of this letter, the Public Health Service, US Department of Health and Human Services and the American Academy of Pediatrics published a joint statement on Thimerosal in vaccines. As the nature of this statement has not required documentation on the toxicity of ethylmercury and the authors of the letter sent to The Lancet made the diagnosis without the prudent evaluation of published data, this survey attempts to fill the gap. It is not concerned with contact allergy or with acrodynia (Pink disease). The only reported case of acrodynia was the result of regular injection of gamma-globulin with ethylmercury preservative to a 20-year-old man who had a history of chronic skin rash and sensitivity to sulfonamide drugs.

KINETICS

Experiments in mice showed no difference between the distribution of ethylmercury chloride and ethylmercurythiosalicylate, but after equivalent doses in mice or rats more mercury was in blood and less in brain after ethyl- than after methylmercury treatment. The passage of methylmercury across the blood–brain barrier is helped by an active transport mechanism whereas passage of ethylmercury is hindered by its larger size and faster decomposition.

The clearance half-time of mercury from the whole body (including gut) of rats was ca. 35 days for both ethylmercury and methylmercury, and mercury cleared from blood with 16 days half-time after the administration of ethyl- and methylmercury. This suggests that in man the 50-day clearance half-time for total mercury after exposure to methylmercury may be valid for ethylmercury. But change in blood mercury concentration indicated faster clearance in four infused patients and slower clearance after occupational exposure. In the following text extrapolation of blood mercury concentration to the end of exposure is based on a 50-day clearance half-time. These clearance half-times are not corrected to the toxicologically important loss of alkylmercury by the cleavage of the alkyl–mercury bond, although, compared with methylmercury 3 days after five daily doses, ethylmercury-treated rats had in blood about 13-fold, in brain 3.6-fold and in kidney 3-fold more inorganic mercury. The difference in decomposition has an effect on the red blood cell to plasma mercury concentration ratio. Although this ratio was 7 in patients poisoned by dietary exposure to methylmercury and 20 after a single oral dose 2-3 weeks after the infusion of ethylmercury it ranged from 2 to 4. Most importantly, when equimolar doses were given to rats, methylmercury caused widespread and ethylmercury only patchy damage in the cerebellar granular. Thus, both kinetic and toxicological studies indicate that the relationships of dose and blood mercury concentration to the risk of intoxication established for methylmercury overestimates the risk of ethylmercury intoxication.

NEUROTOXICOLOGY

None of the signs of ethyl- and methylmercury intoxication are specific. Owing to three large epidemics (two in Minamata and Niagta, Japan, and one in Iraq), very much more is known on the clinical toxicology of methyl- rather than ethylmercury. Thus, in Minamata 100% of the victims had paraesthesia and constriction of the visual field whereas the frequencies of other signs decreased in the following order: ataxia, dysarthria, impaired hearing, tremor. In Niagata the order was similar but the frequencies of constricted visual field and dysarthria were lower and similar. In Iraq the frequency of adverse effects increased when the blood mercury concentration exceeded 0.5 µg ml⁻¹. In the 0.5–1.0 µg ml⁻¹ range 42% of the patients had paraesthesia, 11% had ataxia and 21% had blurred or tunnel vision. The frequencies of dysarthria or hearing defects were 5%. In the range of 3.0–5.0 µg ml⁻¹ 20%