

Thimerosal positivities: the role of organomercury alkyl compounds

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Contact allergy to thimerosal (TH) has not been considered a marker for mercury allergy, since there is a low degree of cross-sensitivity to inorganic as well as to organic mercury salts. 40 subjects, who previously gave a positive patch test reaction only to thimerosal 0.1% pet. (Hermal), when simultaneously repatch-tested to solutions containing TH, mersalyl acid, p-amino-phenylmercuric acid, mercuric acetate and thiosalicylic acid, respectively, gave positive reactions only to TH. 36 out of 40 subjects were divided into 2 groups of 18 subjects and simultaneously repatch-tested to solutions containing TH, methylmercury chloride (MeHgCl), thiosalicylic acid, and, ethylmercury chloride (EtHgCl), respectively. EtHgCl was tested in the 1st group at 0.031% and in the 2nd group at 0.015%. The results showed that all subjects gave concomitant positive reactions to TH, EtHgCl and MeHgCl. EtHgCl 0.031% gave a higher number of +++ reactions than EtHgCl 0.015%, underlining the rôle of the solvent in these reactions. Patch test results in 300 consecutive patients to a standard series, to which MeHgCl was added, showed that MeHgCl and TH were never able to give isolated positive reactions, and that the concomitant positive reactions occurred in only 3.6% of subjects. In conclusion, our data seem to suggest that the positive reactions to TH found in our patients were due to EtHgCl, and that the structural similarities with MeHgCl were so close that the skin reacted against each as if they were identical.

Key words: thimerosal; organomercury alkyl compounds; ethylmercury chloride; methylmercury chloride; allergic contact dermatitis; irritant contact dermatitis; cross-sensitivity. © Munksgaard, 1998.

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Thimerosal (sodium ethylmercurithiosalicylate: TH), when included in patch test standard series, elicits a high frequency of positive reactions. It has been reported that in some countries it is, along with nickel, 1 of the 2 most frequent contact allergens (1). The real nature of the positive patch test reactions to TH has been a matter of debate in recent years and contrasting opinions have arisen over the usefulness of routine patch testing to TH (2, 3). The great majority of the patients patch-test-positive to TH react to ethylmercury chloride (EtHgCl). In a few cases, they react to TH alone or to thiosalicylic acid, which is utilized in the synthesis of TH. In an important review of the meaning of these histologically eczematous positive reactions, Möller pointed out that the high frequency of TH allergy in healthy subjects cannot at present be explained by epicutaneous exposure (4). In addition, since there is a low degree of cross-sensitivity to inorganic as well as to organic mercury salts, contact allergy to TH cannot be con-

sidered a marker for mercury allergy. Recently, we reported that subjects positive to TH alone were not able to cross-react to the 2 organomercury compounds mersalyl acid and p-amino-phenylmercuric acetate (5). The aim of the present paper was to better understand the chemical nature of the compounds responsible for such positive reactions, and to evaluate the usefulness of patch tests to TH.

Materials and Methods

40 subjects, who had previously given positive patch test reactions, without any clinical relevance, only to TH 0.1% pet. (Hermal) included in our standard series, gave their consent to this study. They were simultaneously repatch-tested to 8 µl of the following solutions: TH 0.05% aq., mersalyl acid 0.05% aq., p-amino-phenylmercuric acid 0.05% aq., mercuric acetate 0.05% aq. and thiosalicylic acid 0.05% aq./eth. (50/50). A month later,

36 of the 40 subjects were divided into 2 groups of 18 subjects and simultaneously repatch-tested to 8 μ l of the following solutions, in accordance with the following plan:

Group A: TH 0.05% aq., EtHgCl 0.031% eth., methylmercury chloride 0.031% aq. (MeHgCl), thiosalicylic acid 0.05% aq./eth. (50/50).

Group B: TH 0.05% aq., EtHgCl 0.015% eth., MeHgCl 0.031% aq. thiosalicylic acid 0.05% aq./eth. (50/50).

The concentration 0.031% of EtHgCl corresponds to the amount contained in TH 0.05%; however, since the degree of hydrolysis of TH in vivo has not been determined, EtHgCl was also tested at 0.015%.

300 consecutive patients affected by contact dermatitis were tested to our standard series, to which 8 μ l of MeHgCl 0.031% aq. was added. Patch tests were carried out using A1-test on Leucotest for all the solutions. The panel containing the A1-test was arranged in a vertical row and applied to the back. The distance between the patches was 3 cm. Patch

tests were read in all subjects at D2 and D4 and scored at D2 in accordance with ICDRG guidelines. The substances used were: sodium ethylmercurithiosalicylate (Sigma, purity 98%, MW 404.8), EtHgCl (Alfa, purity 97.7%, MW 265.13), MeHgCl (Erba, purity 98%, MW 251.10), thiosalicylic acid (Aldrich, purity 97%, MW 154.19), mersalyl acid (Sigma, purity 95%, MW 483.9), p-amino-phenylmercuric acetate (Sigma, minimum 80%, MW 351.8).

Results

The 40 subjects tested gave positive reactions only to TH (Fig. 1). Concomitant positive reactions to TH, EtHgCl and MeHgCl were observed in all subjects of *Group A*. EtHgCl 0.031% gave 16 +++ positive reactions (Table 1). Concomitant positive reactions to TH, EtHgCl and MeHgCl were found in all subjects of *Group B* (Fig. 2). EtHgCl 0.015% gave 2 +++ positive reactions (Table 1). In the group of the 300 consecutive patients, 11 subjects



Fig. 1. Thimerosal-positive subjects, when patch tested to organomercury compounds without alkyl groups and to thiosalicylic acid, were unable to give positive responses.

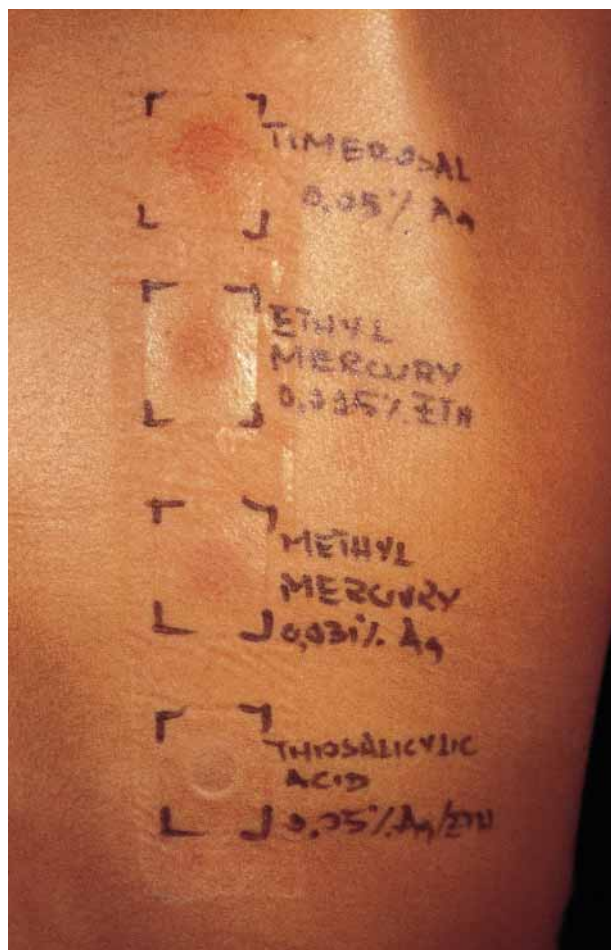


Fig. 2. Concomitant positive reactions to TH, EtHgCl and MeHgCl were observed in subjects positive to thimerosal.

Table 1. Patch test results to organomercury alkyl compounds in 36 thimerosal-positive subjects

Degree of reactions	Group A (18 subjects)			Group B (18 subjects)		
	thimerosal 0.05% aq.	MeHgCl 0.031% aq.	EtHgCl 0.031% eth.	thimerosal 0.05% aq.	MeHgCl 0.031% aq.	EtHgCl 0.015% eth.
+	0	2	0	0	2	2
++	12	15	2	13	14	14
+++	6	1	16	5	2	2

gave concomitant positive reactions to both TH and MeHgCl.

Discussion

Patch test results showed that the 40 subjects reactive to TH were not able to give positive responses either to organomercury compounds without alkyl groups or to thiosalicylic acid. In contrast, EtHgCl and MeHgCl, when applied in 36 out of 40 of the same subjects, always gave concomitant patch test positive reactions. This may indicate that the positive reactions to TH found in our patients were due to EtHg and that the structural similarities between EtHgCl and MeHgCl are so close (the 2 organomercury alkyl compounds differ only by the length of the chain) that the skin reacted against each as if they were identical. However, EtHgCl at concentration of 0.031% in ethanol (the compound is insoluble in water), corresponding to the amount contained in TH 0.05% aq., caused reactions stronger than those elicited by TH and MeHgCl tested at the same concentration, whereas similar degrees of reactions were observed using EtHgCl at 0.015% (Table 1). This difference is probably due to the solvents used, which caused differential penetration of the products, even though we cannot exclude a higher reactivity of EtHg with cutaneous biomolecules.

The question arises as to whether cross-reactivity between TH and EtHgCl was constantly being observed in our patients. Although there are several reports showing that the EtHg component represents the responsible agent in the majority of TH reactions (6–9), the %s of cross-reactivity between TH and EtHgCl reported by various authors were, respectively, 78 (6), 82 (7), 64 (8) and 87 (9). We cannot exclude the possibility that the different findings found in the cited studies and in our study might depend on the system adopted. In all the reported studies, patch tests were performed to thimerosal 0.1–0.05% pet. and to EtHgCl 0.05% pet. In any case, the conclusion that can be drawn from all our tests is that the TH-positive reactions are due to the alkyl organomercury moiety and not to mercury itself.

The patch test results in 300 consecutive patients showed that MeHgCl and TH were never able to give isolated positive reactions, and that concomitant positive reactions occurred in only 3.6% of the subjects tested. Furthermore, the lack of clinical relevance of these reactions, together with the lack of cross-reactivity of TH with other organomercury compounds resulting from our tests, may indicate that the positive reactions to both the organomercury alkyl compounds have mostly to do with their inclusion in the patch test series.

We can reasonably exclude that the patch test reactions to TH occurred in subjects previously sensitized to MeHg. Although MeHg is the most diffuse form of organic alkyl mercury in the environment, the general population is now exclusively exposed to this metal alkyl through the diet (10). It is unlikely that the positive patch test reactions to MeHg depend upon previous consumption of fish. During the Minamata epidemics, for example, contact dermatitis was never reported (11). In addition, although EtHgCl is mostly utilized in the synthesis of TH, and this preservative is widely used in various products for medical use, in cosmetics and as a seed fungicide, it has been considered, experimentally, to be a moderate sensitizer (6).

MeHg and EtHg are more harmful to human health than aryl or inorganic mercury compounds (12). Due to their lipophilicity, they are able to penetrate the skin easily and to move through several biological barriers (10). Wahlberg demonstrated that an aqueous solution of methylmercury dicyandiamide was easily absorbed by the skin in guinea pigs (13). MeHg and EtHg are mostly converted into inorganic mercury in the body (10). It still remains unclear what biochemical mechanisms are involved in mercury toxicity. The lack of this knowledge, as well as the patch test results, do not facilitate finding an answer to the question as to whether these positive reactions are allergic or irritant, and further work is in progress to understand this point. However, since mercury is not an essential metal and since there is therefore no biological requirement, the application of substantial amounts of organomercury alkyl compounds to the back may represent a hazard.

Acknowledgements

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