

# Hypersensitivity to thimerosal: the sensitizing moiety

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There has been increasing interest in characterizing the sensitizing moiety of thimerosal [TIM], following the finding that patients with photosensitivity to piroxicam are allergic to the thiosalicylic acid [TIO] moiety of TIM. For this purpose, the authors have conducted 2 studies in TIM-sensitive patients. In the 1st, of 175 patients tested with TIO and ammoniated mercuric chloride [HGAM], 45.7% reacted only to TIM, whereas 45.7% reacted also to TIO and 17.7% also to HGAM; 9.1% reacted to both TIO and HGAM. In the 2nd, of 47 patients tested with TIO and ethylmercuric chloride [ETHG], 87.2% reacted to ETHG, 44.7% to TIO and 31.9% reacted to both. None of the patients reacted only to TIM. The authors conclude that thimerosal allergy is due either to the mercuric moiety or to thiosalicylic acid, with no cases of sensitivity only to the whole molecule of TIM. TIM-sensitive patients are mainly allergic to the mercuric moiety, but among them there are a large number of TIO-sensitive patients, and these should be advised to avoid piroxicam.

**Key words:** thimerosal; thiosalicylic acid; ethylmercuric chloride; mercury; mercurial compounds; allergic contact dermatitis; piroxicam; photosensitivity. © Munksgaard, 1996.

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Thimerosal (TIM), sodium ethylmercury thiosalicylate, is a preservative used in low concentrations (0.002–0.01%) mainly in vaccines, immunoglobulin solutions, ear, eye and nose drops and, in countries such as ours, also in higher concentrations as a topical antiseptic (0.1% in 50% alcohol – Merthiolate tincture) (1). TIM can induce allergic contact dermatitis in these settings (1–10), but, when we include TIM in a standard series of allergens, we observe many more positive patch tests (10–14), often with no apparent present or past relevance (1, 10–12, 15). Reactivity to TIM occurs at any age, is slightly more frequent in the male sex (11, 12, 15), and is often observed in patients with pompholyx ( $\pm 20\%$ ) and chronic irritant hand dermatitis ( $\pm 19\%$ ) (15), and in healthcare workers (13%) (11, 15).

The first publication on allergic contact dermatitis from TIM dates from 1942 (16), and, since then, there has been interest in characterizing the sensitizing moiety of TIM: mercuric salt (Hg), thiosalicylic acid (TIO), both, or only the whole molecule of TIM (1, 2, 12, 16–19). This concern gained a new dimension with the discovery of the relationship between contact hypersensitivity to TIM and photosensitivity to piroxicam (PRX) (20–22): patients with photosensitivity to PRX are

allergic to the thiosalicylate moiety of TIM (21, 23–25), and about 3/4 of the patients with positive patch tests to TIO, mainly males (25, 26), react to in vitro UVA-irradiated PRX on a patch test or to PRX on a photopatch test, even with no previous contact with this drug (22–27), because of the antigenic similarity between a photoproduct of PRX and TIO (25, 27).

Due to the high frequency of hypersensitivity to TIM (14.2% in 1397 patients) and of photosensitivity to PRX among our patients (35 cases studied), we have had particular interest in characterizing the sensitizing moiety of TIM.

## Patients and Methods

We studied 2 groups of patients with positive patch tests to thimerosal 0.1% pet. (TIM), bought from Trolab or Chemotechnique. The 1st group of patients, tested between 1991 and 1994, consisted of 175 TIM-sensitive patients, 70 males and 105 females, aged between 4 and 74 years (mean 38.3 years). The 2nd group, tested in 1994 and 1995, consisted of 47 other TIM-sensitive patients, 12 males and 35 females, aged between 11 and 80 years (mean 41 years).

All patients were tested with ammoniated mercuric chloride 1% pet. (HGAM), bought from Trolab or Chemotechnique, and with thiosalicylic acid 0.1% pet. Thiosalicylic acid, purchased from Sigma, was analytical reagent grade, confirmed by us with HPLC with UV detection at 220 nm (25). The 2nd group of patients was also tested with ethylmercuric chloride 0.05% pet. (ETHG), kindly supplied by Chemotechnique for patch testing, and, in some cases, with other mercurial compounds: phenylmercuric nitrate (0.01% aq.) (phenylHg) from Trolab, merbromin (2% aq.) (Merb), supplied by the Pharmacy of the Hospital of the University of Coimbra, mercuric chloride (0.1% pet.) (ClHg) and metallic mercury (0.5% pet.) (HG), both from Chemotechnique.

In these studies, allergens were applied on the back, in Leukotest chambers and fixed with Fixomull tape (Beiersdorf) for 2 days. Readings were performed at 2 and 4 days according to ICDRG criteria. Only + and ++ tests were considered.

### Results

In the 1st group of 175 TIM-sensitive patients, 80 reacted only to TIM and were negative to TIO and HGAM (45.7%); 64 reacted to TIM and TIO (36.6%), 15 to TIM and HGAM (8.6%) and 16 to all 3 (TIM, TIO and HGAM) (9.1%) (Table 1). Reactivity to TIO occurred more frequently in the male sex (43 men–61.4%, and 37 women–35.2%).

As HGAM does not seem to be the best com-

*Table 1.* Results of tests with thiosalicylic acid (TIO) and ammoniated mercuric chloride (HGAM) in thimerosal-sensitive patients

Tests	Number	(%)
Total patients	175	
TIO	64	36.6
HGAM	15	8.6
TIO+HGAM	16	9.1
TIM only	80	45.7
TIO (total)	80	45.7
HGAM (total)	31	17.7

*Table 2.* Results of tests with thiosalicylic acid (TIO) and ethylmercuric chloride (ETHG) in thimerosal-sensitive patients

Tests	Number	(%)
Total Patients	47	
TIO	6	12.8
ETHG	26	55.3
TIO+ETHG	15	31.9
TIM only	0	0.0
TIO (total)	21	44.7
ETHG (total)	41	87.2

pound with which to test hypersensitivity to mercury, we tested a 2nd group of patients with the other mercurial compounds. Out of these 47 TIM-reactive patients, 21 reacted to TIO (44.7%), 41 to ETHG (87.2%) and 15 to both substances (31.9%); no patient reacted exclusively to TIM (Table 2). In this group of patients, reactivity to TIO was also more frequent in men (6 males – 50%, and 15 females – 42.8%).

Reactivity to other mercurial compounds was much lower: Merb – 8 cases out of 42 (19%); HGAM – 5 out of 47 (10.6%); ClHg – 4 out of 42 (9.5%); HG – 4 out of 42 (9.5%); and phenyl Hg – 2 out of 38 (5.3%).

### Discussion

Since the first studies characterizing the sensitizing moiety of TIM, there have been differing results, implicating either mainly TIO, the mercuric salt, both, or only TIM (1), depending on the population studied and on the allergens used, namely the mercurial compounds or TIO excipients chosen for testing (10, 12, 17–19).

With the mercurial compounds usually available for testing hypersensitivity to mercury (HGAM, phenylHg, Merb, ClHg, HG), we observed very low reactivity to these salts in TIM-sensitive patients, as reported in the literature (10, 12, 17, 18). These results contrasted with a high reactivity to TIO, and left a large number of TIM-sensitive patients who were allergic only to TIM, as occurred in our 1st group of patients (45.7%) and in previous studies: 20% (10) and 10.8% (17).

Sensitivity to TIO, variable in previous studies (12, 17–19), is higher among our TIM-sensitive patients ( $\pm 45\%$ ), and is high in our population regularly sent for patch testing: 5.9% of 1397 consecutive patients (26). This may be due to particular characteristics of the population or to the excipient used. In preliminary studies, comparing TIO in petrolatum, ethanol and methanol (meth.) at 1 and 0.1%, and in smaller concentrations in methanol, we observed the highest number of positive tests with TIO 0.01% meth. or 0.1% pet. By increasing these concentrations, we merely elicited stronger reactions (personal experience). High reactivity to TIO may explain the frequent observation of photosensitivity to PRX among our patients (21), and its predominance in the male sex may be one of the causes contributing to the higher susceptibility to photosensitivity to PRX in men, as we have previously reported (25, 26).

When we included ethylmercuric chloride in our tests, a mercury salt that is structurally closer to the one in TIM, we observed a much higher reactivity to this mercurial compound (87.2%), simi-

larly to observations in Sweden, 78.9% (12), and Austria, 57.2% and 82% (18, 19).

In our 2nd study, there was no residue of cases with sensitivity only to TIM, which contrasts with the Austrian experience, where 40% of patients reacted only to TIM (18, 19), or the study by Möller, where 2/23 patients reacted only to TIM (12). This may be due to the diluent used to test TIO in the 1st case (ethanol) (18, 19), or to the salt of TIO used by Möller (ethylmercuric thiosalicylsulfonate) (12).

### Conclusions

The best way to characterize the moiety of TIM responsible for hypersensitivity is to patch test such patients with TIO 0.1% pet. and ETHG 0.05% pet.

According to our studies, hypersensitivity to TIM is due either to the mercurial moiety, to TIO, or to both, and there is no reactivity exclusively to the whole molecule of TIM. Ethylmercuric chloride is the responsible agent in most cases of hypersensitivity to TIM (87.2%), but we must pay special attention to the 45% who are allergic to TIO, because they should be advised to avoid piroxicam.

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