Thimerosal Allergy and Clinical Relevance in Thailand

Penpun Wattanakrai MD*,
Natta Rajatanavin MD*

** Division of Dermatology, Department of Medicine, Ramathibodi Hospital, Mahidol University*

Background: *Thimerosal or merthiolate is used as an antiseptic and a preservative in topical medicaments, cosmetics, and vaccines. Thimerosal is known to cause delayed type hypersensitivity. However, there is argument about the clinical relevance and risk of using thimerosal-preserved products in thimerosal allergic individuals.*
Objective: *Retrospective review of patch test results from the Ramathibodi Hospital patch test clinic to determine the prevalence and relevance of allergic reactions to thimerosal in Thailand.*
Material and Method*: During a 5-year period, thimerosal was patch tested in all patients tested for possible allergic contact dermatitis. Thimerosal was the second most common allergen causing a positive patch test reaction.*
Results: *Of the 433 patients tested, 46 (10.62%) were positive to thimerosal. However, despite the high prevalence of positive reactions none was clinically relevant to their present dermatitis, none of the patients reported reactions to vaccination or cross-reaction to piroxicam.*
Conclusion: *There was a high rate of sensitization to thimerosal in Thai patients, but were of little clinical relevance. The author does not advise thimerosal allergic individuals to avoid vaccination, although the small risk of local dermatitis should be pointed out. The topical use of thimerosal containing antiseptics should be avoided.*

Keywords: *Allergic contact dermatitis, Patch test, Thimerosal, Merthiolate*

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Thimerosal (merthiolate) contains two compounds: an organic mercury compound and a thiosalicylate compound. This organic mercurial derivative of thiosalicylic acid has been used as a topical antiseptic and effective preservative in numerous medical and non-medical products since the early 1930s. It is used as a preservative in some cosmetics, ophthalmic and otolaryngology medication, vaccines, antitoxins, topical and intramuscular steroid preparations, and intradermal tests[1,2]. Reactions to thimerosal can cause delayed type hypersensitivity reactions (contact dermatitis, systemic contact dermatitis), type I hypersensitivity, mercury poisoning, acute and chronic cumulative mercury toxicity[1,3,4] but there is much disagreement about the clinical relevance of allergy to thimerosal[2,5]. Piroxicam photosensitization may occur in thimerosal - sensitive individuals due to cross-reactions between thiosalicylate and piroxicam[1,6]. Reports have shown the prevalence of thimerosal allergy to range widely between different countries[7-14]. In the present report, the authors reviewed the prevalence and clinical relevance of thimerosal allergy in Thai patients sent for patch testing in the evaluation of allergic contact dermatitis.

Correspondence to : Wattanakrai P, Division of Dermatology, Department of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand.

Material and Method

The present study was a 5-year retrospective analysis of patch test results of patients with suspected allergic contact dermatitis patch tested in Ramathibodi patch test clinic from 2000 to 2004. Thimerosal was tested as 0.1% in petrolatum, with 29 other allergens on the standard screening tray all purchased from Chemotechnique Diagnostics AB (Malmo, Sweden). The patients were patch tested using a standardized technique with Finn chambers (Epitest Ltd Oy, Tuusula,

Table 1. Gender in thimerosal allergy

Gender	Number Patch tested N (%)	Thimerosal Positive N(%)	Skin hyperactivity (Angry back)[15]
Female	343 (79.2)	40 (86.9)	2
Male	90 (20.8)	6 (13.1)	1
Total	433 (100.0)	46 (100.0)	3

Finland) on Scanpor tape (Norgesplaster Aksjesxelskap, Venesia, Norway). The patches remained in place for 48 hours, and test sites were evaluated twice at 48 and 96 hours after initial placement. A positive patch test result was interpreted to be a 1+, 2+, 3+ reaction as defined by the International Contact Dermatitis Research Group (ICDRG). The results were presented in the frequency tables with numbers (%).

Results

Of the 433 patients patch tested, 49 patients had an allergic reaction to thimerosal. Three of these reactions were interpreted as multiple false positive patch test reactions caused by skin hyperactivity (excited skin syndrome or "angry back"[15]) so were excluded from further analysis. This left 46 (10.62%) patients from 433 tested with allergic reaction to thimerosal. The frequency of positive patch test to thimerosal was 11.66% in women (40 of 343 women tested) and 6.67% in men (6 of 90 men tested). With 86.95% (40 in 46) of the thimerosal sensitized patients being females (Table 1).

The age distribution of thimerosal allergic patients ranged between 5-58 years old (mean 32.5 years) and is shown in Table 2.

Occupation of patients sensitized to thimerosal is shown in Table 3. A predominance in three occupation groups: secretarial/office workers, students and health care workers was noticed. The locations of presenting dermatitis sent for patch testing in thimerosal positive patients are shown in Table 4.

In evaluation of the clinical relevance of the positive thimerosal reactions, none of the reactions was currently relevant to the present dermatitis. None of the thimerosal allergic patients reported cross-reactions to piroxica or significant vaccine reactions, although some patients, when questioned, did recall some local pain/induration at vaccine injection sites. One patient had possible past relevance with a history of reaction to both hard and soft contact lenses usage. Four patients had a probable past relevance with a

Table 2. Age group in thimerosal allergy

Age (years)	Number of patients (%)
< 20	9 (19.6)
20-30	10 (21.7)
30-40	13 (28.3)
> 40	14 (90.4)
Total	46
Range (yrs)	5-58
Mean (yrs)	32.5

Table 3. Occupation in thimerosal allergy

Occupation	Number of patients(%)
Secretarial/office workers	14 (30.4)
Students	13 (28.3)
Health care workers	10 (21.7)
Merchant	3 (6.5)
House keeper	2 (4.3)
Drivers	2 (4.3)
Metal worker	1 (2.2)
Dressmaker	1 (2.2)
Total	46 (100.0)

Table 4. Location of dermatitis (Some had skin lesions on more than 1 site)

Location	Number (%)
Hands	13 (28.3)
Face	12 (26.1)
Generalized	6 (13.0)
Hands and feet	3 (6.5)
Arms/legs	2 (4.3)
Lips	5 (10.9)
Buccal mucosal (Lichen planus)	2 (4.3)
Others	6 (13.0)

history of dermatitis to topical tincture merthiolate or mercurochrome. One patient frequently applied tincture of merthiolate to her hand eczema and reported no problem. Two patients presenting with oral lichen planus and suspected allergic contact dermatitis to dental amalgam; which contains mercury, were confirmed with positive patch test to amalgam and mercury. Both these positive reactions to thimerosal were interpreted as cross-reactions from the mercury compound in thimerosal.

Table 5. Thimerosal sensitization reported in different countries

Country	% Positive patch test results to thimerosal
Austria[7]	11.8
NACDG[8]	10.09
Japan[9]	9.5
Spain[10]	5
Germany[11]	4.7
Canada[12]	4.53
Switzerland[13]	4.2
Denmark[14]	3
Sweden[14]	4
Thailand (Ramathibodi)	10.62

Discussion

Reports of thimerosal sensitization widely range between different counties[7-14] (Table 5). The frequency and prevalence of thimerosal sensitization has been found to increase over the last few years, and it commonly affects children and young adults[2,5]. The common sources of exposure to thimerosal include; topical antiseptics, preservatives in contact lens solution, eye/nasal/ ear drops, and dental amalgam restoration with vaccinations being the most blamed culprit responsible for the increasing sensitization in younger age groups[16-19].

The prevalence of thimerosal sensitization in Thailand has not been reported before. There was a high prevalence of thimerosal allergy of 10.62% in the presented patients sent for routine screening patch test but none was clinically relevant to their present dermatitis.

Reports have shown that occupational risks for thimerosal allergy include; health care workers[20,21], food handlers, and secretarial workers[2]. Females are also associated with a higher incidence of allergy to thimerosal[2]. The presented patient group also coincided with these previous observations with 40 of 46 (86.96%) patients being female (Table 1).

In the present series, there was a higher incidence of thimerosal allergy in three occupational groups; secretarial, students, and healthcare workers (Table 3). For office workers, this may be because most were female. Healthcare workers, also predominantly females, may be sensitized through more frequent vaccinations or contact with topical antiseptics. Students, representing the younger age group, most likely are asymptomatically sensitized to thimerosal because of increasing vaccination schedules as reported by others[16-19].

The present study demonstrates the fact that despite the high percentage of thimerosal - allergic patients, none of these reactions was clinically relevant to the patient's skin condition. This has also been observed by others[2] and because of its frequent positive but often irrelevant reaction when patch tested thimerosal has been coined "contact non (allergen) of the year 2002"[5] Though hypersensitivity to thimerosal in vaccine has been reported to cause persistent local reactions, systemic contact dermatitis, urticarial to generalized exanthematous reactions, urticaria and asthma[3,24,25] many others report that vaccines do not cause problems[26-28]. None of the presented patients reported significant vaccine reactions and the presented patients were not instructed to avoid vaccination. Audicana et al[10] conducted an intramuscular thimerosal challenge test in 57 thimerosal patch test positive patients. In this challenge, the needle used for aspiration of the thimorosal solution from the bottle was discarded and replaced by a new needle before injection to avoid contamination of the dermis. Results showed that only five of the 57 patients (9% of thimerosal positive reactions) experienced a mild local reaction of local induration, micropapules that resolved with topical steroids. The other 52 of 57 patients (91%) tolerated the intramuscular challenge test with thimorosal.

Thimerosal is on the TRUE Test screening allergen panel (Glaxo Dermatology), the North American Contact Dermatitis Group (NACDG) and Japanese Society for Contact Dermatitis (JSCD) standard allergen panels, but is not among the 22 allergens tested on the European standard series as recommended by the European Environmental and Contact Dermatitis Research Group (EECDRG). In Thailand, there is no recommended standard screening allergen series for evaluation of patients with suspected allergic contact dermatitis. In the Ramathibodi patch test clinic, the authors tested 30 allergens including thimerosal in the

standard allergen tray. However, because the authors found that thimerosal reactions were usually irrelevant, it was removed. Furthermore, most relevant allergic reactions are easily suspected clinically in patients with dermatitis. They are directly correlated with sites of application of topical ophthalmologic/otologic medications or antiseptics containing thimerosal[3]. Therefore, if suspected, thimerosal can be additionally patch tested.

Lists of products containing thimerosal have been reviewed[2,3] but thimerosal free products are not provided. For doctors and consumers in Thailand, lack of labeling of ingredients in cosmetics, topical medications, and vaccines makes it very difficult to know if a product contains thimerosal. This review demonstrates that most thimerosal patch test positive reactions are irrelevant and have low clinical significance. However, due to the debate of early sensitization during childhood vaccines and attention for a reduction of children's exposure to mercury, the use of thimerosal in vaccines and pharmaceutical sources tend to be reduced or eliminated[4,29,30]. In the authors' clinic, the authors do not advise the patients to avoid the benefits of vaccination although the small risk of local dermatitis is pointed out. However, because of many other simple alternatives for topical antiseptics, the authors recommend that the use of thimerosal containing antiseptics should be avoided.

The authors hope that this review will help decrease the patient and doctor's concern of these frequent but irrelevant positive patch test reactions to thimerosal and they should be considered with little clinical significance.

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ผื่นแพ้สัมผัสต่อไธเมอโรซาล และความสำคัญทางคลินิกในประเทศไทย

เพ็ญพรรณ วัฒนไกร, ณัฏฐา รัชตะนาวิน

ภูมิหลัง: *ไธเมอโรซาล (thimerosal) หรือ เมอร์ไธโอเลท (merthiolate) ใช้เป็นยาระงับเชื้อ และวัตถุกันเสียในยาทาผิวหนัง เครื่องสำอาง และวัคซีน thimerosal ก่อให้เกิดการแพ้แบบ delayed type hypersensitivity แต่ความสำคัญทางคลินิก และความเสี่ยงจากการใช้ผลิตภัณฑ์ที่มี thimerosal ผสมอยู่ในผู้ที่ทดสอบทางผิวหนังว่าแพ้ thimerosal ยังไม่เป็นที่แน่ชัด*

วัสดุและวิธีการ: *รายงานนี้เป็นการวิจัยย้อนหลังห้าปีในคลินิกผื่นแพ้สัมผัสโรงพยาบาลรามาธิบดี เพื่อหาอุบัติการณ์และความสำคัญทางคลินิกของผื่นแพ้สัมผัสต่อ thimerosal ในคนไทย*

ผลการศึกษา: *พบว่า thimerosal เป็นสาเหตุอันดับ 2 รองจากโลหะนิเกิล ของผลทดสอบเป็นบวก ในผู้ถูกทดสอบทั้งหมด 433 ราย มีผู้ป่วย 46 ราย (10.62%) ที่มีผลทดสอบเป็นบวกต่อ thimerosal ซึ่งไม่พบผู้ใดมีความสัมพันธ์กับผื่นผิวหนังในปัจจุบัน และไม่พบผู้ใดมีปฏิกิริยาแพ้การฉีดวัคซีนหรือมีปฏิกิริยาแพ้ร่วมต่อ piroxicam*

สรุป: *ผู้เขียนจึงไม่แนะนำให้ผู้ที่ทดสอบทางผิวหนังว่าแพ้ thimerosal หลีกเลี่ยงการฉีดวัคซีน แม้จะมีโอกาสเกิดปฏิกิริยาเฉพาะที่บริเวณผิวหนังได้ แต่ควรแนะนำให้ใช้ยาทารักษาอาการติดเชื้อที่ผิวหนังชนิดอื่นแทน thimerosal*