Adverse Reactions to Tetanus Toxoid

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• **A retrospective review of 740 charts of patients with a history of adverse reaction to tetanus toxoid immunization was undertaken. The most common reactions, by history, were local edema and tenderness (33%), fever (15%), and anaphylactoid response (33%). Three patients who had a vesicular eruption at the immunization site were found to have delayed hypersensitivity to mercury. Thirty percent of the patients had received tetanus toxoid within one year and 55% within five years of evaluation. Reactive responses to immediate skin tests were exceedingly rare (<1%). None of the challenge patients suffered an adverse reaction.**

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TETANUS and diphtheria cause serious health problems throughout the world.[1-3] Nonimmunized populations are at risk to contract either disease, since *Corynebacterium diphtheriae* and *Clostridium tetani* are found widely dispersed on man or in his environment. The World Health Organization estimates that more than 500,000 deaths a year are caused by tetanus or complications of this disease.[4] Reported cases and deaths from tetanus in the United States during the decade 1966 to 1976, compiled from the Centers for Disease Control's *Morbidity and Mortality Weekly Report*, show a downward trend in the number of yearly cases, but have still a mortality approximating 50%.[5] Sporadic cases of diphtheria are reported with isolated epidemics occurring in certain populations of nonimmunized persons.[3] Both diseases are preventable with appropriate immunizations. Protection is long-lasting after a primary series and each subsequent booster immunization; however, periodic booster immunization is necessary as antitoxin titers wane.

Adverse reactions of many types have been reported since the use of these immunizations became widespread. Tetanus toxoid is the immunization associated with the overwhelming majority of reactions.[6-9] The significance of these reactions to tetanus toxoid is often unclear to the primary-care provider, resulting in avoidance of an extremely important and effective immunization. The difficulty in obtaining a commercial source of diphtheria toxoid separate from tetanus toxoid results in avoidance of this immunization as well.

The purpose of this study was to determine any correlation of the adverse-reaction history, the skin test response, the interval from last immunization, and the response to a controlled challenge of tetanus toxoid.

MATERIALS AND METHODS

Patient Selection

Since the armed forces require these immunizations to enter active duty, all personnel entering the US Air Force since 1970 who responded positively to questions concerning adverse reactions to tetanus toxoid were included in the study.

Historical Data Points

A historical data sheet was completed by each patient with emphasis on the following: age at time of the reaction; symptoms and time-frame of the reaction; duration from last immunization; and personal and family history of atopic diseases.

Skin Tests

Serial tenfold-dilution intradermal skin tests using commercially prepared plain tetanus toxoid were performed (Table 1). Following a negative 1:100 v/v intradermal test result, a subcutaneous challenge was begun using diphtheria and tetanus toxoids, adsorbed. Saline-negative control and histamine-positive 1:1,000 (0.01 mL) control intradermal skin tests were performed in all patients. The challenge was suspended for 24 hours following a 0.1-mL full-strength injection to monitor for delayed reactivity. Criteria for skin test interpretation are as listed (Table 2).

RESULTS

Sex, Age, and Atopic Background

Male to female ratio was 4:1, and 98% of the subjects were 17 to 27 years of age at the time of evaluation, reflecting the military recruit population. A subjective personal history of atopy was noted in 12% and a family history of atopy was related by 15% of the subjects.

Adverse Reactions

By history, a multitude of adverse reactions were ascribed to tetanus toxoid immunizations (Table 3). Anaphylactoid reactions are those occurring within two hours of the immunization and consisting of urticaria-angioedema, shortness of breath and wheezing, sneezing and pruritus to the nose and eyes, or symptoms consistent with a hypotensive episode. The largest group are those in whom local edema, erythema, and tenderness developed, which persisted from two to five days.

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The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Air Force or the Department of Defense.

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Table 1.—Skin Test and Challenge Schedule*

Volume, mL	Dilution	Route
Plain tetanus toxoid		
0.02	1:100,000	Intradermal
0.02	1:10,000	Intradermal
0.02	1:1,000	Intradermal
0.02	1:100	Intradermal
Diphtheria and tetanus toxoids, adsorbed		
0.02	1:10	Subcutaneous
0.1	1:10	Subcutaneous
0.1	Full strength	Subcutaneous
0.4	Full strength	Subcutaneous

*Test every 15 minutes. Delay full immunizing dose until reading 0.1-mL full-strength challenge for delayed hypersensitivity.

Table 2.—Skin Test Criteria

Score	Sign
1+	<4 mm wheal
2+	4-7 mm wheal
3+	8-10 mm wheal
4+	>10 mm wheal or pseudopodia

Table 4.—Interval From Adverse Reaction in Relation to Immediate Skin Test Results

Interval	No. (%) of Patients	No. of Patients With Positive Immediate Skin Test Result
<1 yr	222 (30)	1
1-5 yr	185 (25)	0
6-10 yr	111 (15)	0
>10 yr	222 (30)	3

Vesicular eruption on left deltoid area demonstrating type IV hypersensitivity to mercury-containing preservative, thimerosal, in diphtheria and tetanus toxoids, adsorbed, administered with jet injector apparatus.



Table 3.—Adverse Reactions to Tetanus Toxoid Immunization

Symptom*	No. (%) of Patients
Anaphylactoid reaction	95 (13.0)
Local swelling, erythema, and tenderness	248 (33.6)
Immediate (<2 hr)	64 (8.7)
Delayed (4-8 hr)	37 (5.0)
Late (>12 hr)	75 (10.1)
Unknown time-frame	72 (9.8)
Fever	113 (15.3)
Immediate (1-3 hr)	30 (4.1)
Delayed (>4 hr)	83 (11.2)
Nausea and vomiting	84 (11.4)
Constitutional symptoms (malaise, fatigue, etc)	57 (7.8)
Generalized nonspecific rash	38 (5.2)
Acute dizziness	22 (3.0)
Syncope	11 (1.5)
Arthralgias	7 (1.0)
Miscellaneous	(Each <1)
Localized urticaria at injection site; infection at injection site; vesicles at injection site; phlebitis; "shock" (delayed time-frame); seizure; "red spots all over arms"; "sleepwalking"; "chest-wall swelling" (delayed); "hallucinations"; paralysis (generalized, transient)	

*Several patients described more than one symptom and data are therefore presented as a percentage of total complaints.

Interval From Adverse Reaction

Fifty-five percent (407/740) of the patients had experienced the adverse reaction within five years of evaluation; however, 30% (222/740) of the patients had reacted in childhood and not received a tetanus immunization for more than ten years (Table 4).

Skin Tests and Challenge

Seven-hundred thirty of 740 patients were nonreactive to skin testing and challenge. Ninety-four of 95 patients with anaphylactoid symptoms had a negative response to the skin test and tolerated the challenge without reaction. One patient with anaphylactoid symptoms (Table 5, patient 3) had immediate skin reactivity but tolerated a full immunizing dose without adverse effects. Patient 4, who had experienced a syncopal episode, reacted to skin testing in the immediate time-frame, but tolerated the full challenge without difficulty. Patients 1 and 2, with histories of local edema in the delayed time-frame, had immediate skin test responses and refused the challenge phase.

Edema, erythema, and tenderness to injection sites that persisted beyond 24 hours before resolving without treatment developed in patient 2 and a patient whose responses to the testing and challenge were negative.

Patients 5 to 7 complained of a weeping, vesicular reaction at the injection site (Figure) with underlying edema, erythema, and tenderness. Skin testing disclosed delayed reactivity to diphtheria and tetanus toxoids, adsorbed. Patch-testing response was positive to mercury and thimerosal and negative to plain tetanus toxoid.

Patients 8 to 10 were inadvertently challenged intradermally with 0.1 mL of full-strength tetanus toxoid and had development of large local indurated erythematous lesions at the site that persisted for several days.

COMMENT

Numerous reports of adverse reactions to tetanus toxoid have appeared in the past two decades.[7-13] One proposed explanation for many of these reactions is the existence of high titers of tetanus antitoxin antibody at the time of reimmunization.[12-13] Factor et al[14] examined a group of tetanus-immunized persons who had no history of adverse reactivity to tetanus toxoid. Using undiluted intradermal skin tests they reported an alarming degree of skin reactivity in the immediate, Arthus, and delayed time-frame and implied a danger of significant systemic reactions. Skin testing with concentrated materials, including tetanus toxoid, has been reported to cause skin reactivity within these time-frames by numerous investigators.[8,15-17] The reactions

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Table 5.—Data for Skin Test Reactivity* in Ten Study Patients

Patient No.	Reaction	Onset	Duration	Interval Since Reaction	Skin Test Dilution 1:10,000	1:1,000	1:100	1:10	Full Strength
1	Local edema	Delayed	4 Days	>10 yr	−	−	++	. . .	. . .
2	Local edema	Delayed	7 Days	1 mo	−	+++	. . .	. . .	. . .
3	Diffuse urticaria	Immediate	Unknown	>10 yr	+	++	++	−†	−†
4	Syncope	Immediate	Hours	>10 yr	+++	+	++	−†	−†
5	Local vesiculation	Delayed	5 Days	1 mo	−	−	−	−	++‡
6	Local vesiculation	Delayed	7 Days	1 mo	−	−	−	−	+++‡
7	Local vesiculation	Delayed	4 Days	1 mo	−	−	−	−	++‡
8	Unknown	Unknown	Unknown	>10 yr	−	−	−	−	+++‡
9	Unknown	Unknown	Unknown	7 yr	−	−	−	−	++++‡
10	Fever	Delayed	4 Days	1 yr	−	−	−	−	++‡

*−indicates negative response; +, equivocal response; ++, mildly positive response, +++, positive response; ++++, strongly positive response.
†Indicates subcutaneous skin test; all others were intradermal.
‡Read at 24 hours.

are thought to represent nonspecific irritation within the immediate time-frame and recognition by the cellular immune system when in the delayed time-frame, but not indicative of allergic sensitization. This recognition phenomenon is demonstrated in patients 8 to 10 (Table 5) who were inadvertently tested intradermally to full-strength solutions.

All 95 patients with histories suggestive of a prior anaphylactoid reaction tolerated full immunizing doses of diphtheria and tetanus toxoids, adsorbed. Of the 740 patients who reported a prior adverse reaction to tetanus toxoid, skin testing and challenge failed to document a single case of hypersensitivity of the immediate type. Two of the four patients who reacted to skin testing within the immediate time-frame underwent a full challenge without adverse effects. The remaining two patients, 1 and 2 (Table 5), refused a challenge; however, the skin test responses of 246 patients with an identical reaction-history were negative, and all tolerated full immunizing doses of tetanus toxoid. Additionally, 50% of the adverse reactions had occurred within five years and 30% had occurred within a year of testing-challenge in our clinic and, yet, failed to demonstrate immediate reactivity. These factors suggest mechanisms other than IgE antibody for the adverse reactions in the group and the minimal degree of reactivity in the individuals with skin-test response.

Three patients did demonstrate, through the cellular immune system, hypersensitivity to mercury, which is found as the preservative, thimerosal, 1:10,000, in diphtheria and tetanus toxoids, adsorbed, and in fluid tetanus toxoid preparations. This sensitivity to mercury should not preclude the use of tetanus and diphtheria immunizations, since only local cell-mediated (type IV) hypersensitivity is anticipated and can be treated.

In those patients who demonstrate immediate skin test reactivity, a conservative and safe approach is to measure antitoxin titers to determine need for a booster. Should a booster be required, the patient must be in a setting with proper equipment for treatment of anaphylaxis. The exceedingly rare patient with an anaphylactoid reaction, historically, and a skin test response that increases with higher concentrations must be considered a high-risk patient in whom the challenge phase is contraindicated.

The following conclusions were drawn from this chart review:

1. Immediate skin test reactivity and immediate hypersensitivity are exceedingly rare to tetanus and diphtheria toxoids, adsorbed, in a controlled testing-challenge technique.

2. The history and the interval since the immunization of the adverse reaction did not correlate with the testing and challenge.

3. A history of an adverse reaction to tetanus toxoid does not preclude future immunization to this same material.

4. The only hypersensitivity in this population was type IV to thimerosal (a mercury-containing preservative) causing edema, tenderness, and redness with skin vesiculation at the injection site and does not preclude the use of tetanus and diphtheria toxoids.

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