

Original article

Adverse reactions to tetanus toxoid

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Background: Systemic and, in particular, local adverse reactions after the administration of tetanus toxoid are frequent. Type I, III, and IV immunological mechanisms have been implicated in the pathogenesis of these reactions. The objective of this study was to determine the characteristics of patients referred to our center because of adverse reactions following the administration of tetanus toxoid as well as to assess the suitability of a diagnostic protocol that included to perform skin tests with tetanus toxoid and merthiolate. **Methods:** A total 20 patients who sought medical care because of systemic reactions and 15 patients because of local reactions to tetanus toxoid were reviewed. Specific IgG antibodies against tetanus toxoid were determined and patch test and intradermal reaction with merthiolate and skin tests (prick test and intradermal reaction) with tetanus toxoid were performed. In those cases in which it was deemed necessary, a desensitization schedule was instituted. **Results:** Most patients showed protecting titers IgG antibodies. The study of hypersensitivity to merthiolate was negative in all cases. Skin tests with tetanus toxoid were positive in 73% of patients who had developed local adverse reactions and in only 23% of those who had suffered from systemic reactions. **Conclusions:** In cases of systemic reactions to tetanus toxoid, skin tests have a high negative predictive value since all patients with systemic reaction and negative studies tolerated re-administration of the compound. None of the patients with delayed local reaction and positive results tolerated desensitization, so that it does not seem to be useful in the case of such reactions.

KEY WORDS: **Tetanus toxoid / Hypersensitivity / Skin tests / Desensitization.**

Reacciones adversas por toxoide tetánico

Fundamento: La aparición de reacciones adversas, sobre todo locales pero también sistémicas, debidas a la administración de toxoide tetánico son frecuentes. En la patogenia de estas reacciones se han implicado mecanismos inmunológicos de tipo I, III y IV. El objetivo de este estudio ha sido analizar las características de los pacientes remitidos por haber presentado reacciones adversas tras la administración de toxoide tetánico y valorar la rentabilidad de un protocolo diagnóstico que utiliza pruebas cutáneas frente a toxoide tetánico y merthiolate. **Métodos:** Se revisaron 20 consultas por reacciones sistémicas y 15 consultas por reacciones locales. Se determinaron anticuerpos IgG específicos frente a toxoide tetánico, se realizaron pruebas epicutáneas e intradermorreacción frente a merthiolate y pruebas cutáneas (*prick test* e intradermorreacción) frente a toxoide tetánico. En los casos necesarios se realizó una pauta de desensibilización. **Resultados:** La mayoría de los pacientes tenían títulos protectores de anticuerpos IgG específicos. El estudio de hipersensibilidad a merthiolate fue negativo en todos los casos. Las pruebas cutáneas a toxoide tetánico fueron positivas en el 73% de los pacientes que habían sufrido reacciones locales y sólo en el 23% de los que habían sufrido reacciones sistémicas. **Conclusiones:** En los casos de reacciones sistémicas, las pruebas cutáneas tienen un alto valor predictivo negativo, ya que todos los pacientes con reacciones sistémicas y estudio negativo toleraron la readministración. Ningún paciente con reacción local retardada y estudio positivo toleró la desensibilización, por lo que no parece ser útil en el caso de estas reacciones.

PALABRAS CLAVE: **Toxoide tetánico / Hipersensibilidad / Pruebas cutáneas / Desensibilización.**

Immunization with tetanus toxoid (TT) is a part of the vaccination calendar offered in childhood, and booster doses are recommended at ten-year intervals. The most frequent adverse reaction is a local one, characterised by pain and tenderness in

the zone of injection occurring in 50-85% of all immunizations, erythema and oedema in 20-30% and more seldom, in less than 2%, marked oedema and tumefaction¹. Anaphylactic reactions are extremely infrequent: in a total of 15,752 doses

Table I. Patients characteristics

Type of reaction	No. of patients	Gender		Mean age (range) ^a	Atopic antecedents	Mean elapsed time (range) between reaction and study (years) ^a
		M	F			
Local	15	2	13	48,3 (7-74)	2	1,9 (0,4-6)
Systemic	13	5	8	24 (6-53)	1	14 (0,4-43)

M: Male; F: Female

^aYears

administered to children under six years not a single case was detected², and the incidence in adults has been 0.001% after 158,230 doses³. However, in a retrospective study of 740 adverse reactions 13% were considered to be anaphylactoid, although the skin tests were positive in less than 1% of the cases⁴. Non-immunologic neurological reactions are relatively frequent after administration of TT in association to Pertussis toxoid in children. These reactions range from mild ones (somnolence, irritability, vomiting and febrile syndrome) to severe neurologic complications (simple febrile seizures, hypotonia, encephalopathy and death).

The aim of the present study was to analyse the characteristics of patients referred because of adverse reactions after administration of tetanus toxoid, and to assess the cost-effectiveness of the diagnostic protocol used at our Service.

MATERIAL AND METHODS

Patients. The study initially encompassed 35 patients referred to our Service because of adverse reactions after the administration of TT. Fifteen patients had consulted because of local reactions (erythema and tumefaction), which was immediate in 30% of the cases, occurred within the first two hours in 20%, and was delayed (over 24 hours) in 50%.

Twenty patients consulted because of systemic reactions: eight reported generalised urticaria, four exanthemas, one had developed dyspnoea, two loss of consciousness, four febrile seizures and one irritability. All cases with clinical features not suggestive of an immunological mechanism (n = 7) were excluded from the study (most of these cases were children with reactions after DTP vaccination). The remaining 13 patients had eviden-

ced immediate reactions in 27% of the cases, within two hours in 27%, and delayed reactions (over 24 hours after administration of TT) in 46% of the cases.

The characteristics of the patients are summarised in Table I.

Laboratory findings. The specific TT IgG serum levels were measured (enzyme-linked immunoassay [EIA], detection limit, 0.01 U/ml). Titres in excess of 0.1 IU/ml were considered to be protective.

Skin tests. Epicutaneous tests were performed with merthiolate (0.1% in petrolatum), and read after 48 and 96 hours.

Prick tests. Skin prick tests were performed with prick test lancets with a 1-mm point (DHS, Bayer). Histamine hydrochloride (10 mg/dl) was used as the positive control and normal saline as the negative one. The tests were read after 15 minutes, and wheals ≥ 3 mm in diameter were considered positive.

Intradermal tests. These were performed with intradermal injection of 0.02 ml TT, to achieve a 3-mm papule. The tests were read after 20 minutes, with late reading after 24 hours; normal saline was used as the negative control. The test was considered to be positive when the initial papule

Table II. Desensitization / tolerance protocol

Dose ^a	Volume (ml)	Dilution	Route
1.	0,02	1:1000	ID
2.	0,02	1:100	ID
3.	0,02	1:10	SC
4.	0,05	1:1	SC
5.	0,10	1:1	SC
6.	0,15	1:1	SC
7.	0,20	1:1	SC

^aDoses injected at 20-minute intervals.

IDR = intradermal; SC: subcutaneous.

Table III. Patient characteristics and study results in the cases with previous local reactions

Case No.	Gender	Age (years)	Latency	Elapsed time (years)	Serology (UI/ml)	TT prick	TT intradermal	Tolerance/desensitization
1	F	70	> 24 hours	6	0,46	Negative	+ Delayed	Delayed reaction
2	F	36	?	?	1,16	+ Immediate	N.P.	N.P.
3	F	52	?	1	N.P.	Negative	+ Delayed	Delayed reaction
4	M	43	?	1	N.P.	Negative	Negative	Yes
5	F	42	Immediate	1	0,49	Negative	Negative	N.P.
6	F	57	Immediate	0,5	2,79	Negative	+ Immediate	N.P.
7	M	7	> 24 hours	0,2	N.P.	Negative	+ Delayed	N.P.
8	M	33	Hours	0,5	2,12	Negative	+ Delayed	N.P.
9	F	35	> 24 hours	?	Negative	Negative	+ Delayed	N.P.
10	F	66	?	4	0,40	Negative	Negative	Delayed reaction
11	F	40	Hours	4	0,97	Negative	Negative	N.P.
12	F	74	> 24 hours	0,3	0,75	Negative	+ Delayed	Delayed reaction
13	F	69	> 24 hours	5	9,11	Negative	+ Immediate	N.P.
14	F	42	Hours	3	Negative	Negative	+ Immediate	N.P.
15	F	59	Immediate	1	0,99	Negative	+ Immediate	N.P.

M = male; F = female; TT = tetanus toxoid; N.P. = not performed; ? = unknown; + = positive.

doubled in size, or when a papule ≥ 6 mm in diameter was elicited. These tests were carried out with merthiolate (Ifidesa-Aristegui, 0.001%) and with 1/1000 and 1/100 tetanus toxoid (Anatoxal Te Berna: 12.5 Lf/0.5 ml and 0.01% merthiolate).

Subcutaneous re-exposure or progressive desensitization were carried out according to the protocol described by Carey and Meltzer⁵ (Table II). This was always begun when the patient was asymptomatic, with blood pressure, heart rate and respiratory rate controls prior to starting and at 20-minute intervals thereafter. The same procedure was used in all cases; only the designation was changed from desensitization to re-exposure when the study had been negative.

RESULTS

Most patients (83% of those consulting for local reactions, and 66% of those consulting for systemic ones) evidenced protective titres of TT antibodies. The merthiolate hypersensitivity studies (both the epicutaneous and the intradermal tests) were negative in all cases.

Local reactions (Table III). The prick test was immediately positive in 6% (1/15) of the patients; this patient refused pursuing the study. Ten out of 13 (77%) intradermal tests were positive, immediately in four cases and after 24 hours in six. Among the four patients with negative study, one

tolerated the subcutaneous re-exposure, one developed a delayed local reaction after 24 hours, and in two cases no desensitization was performed as they evidenced protective antibody titres. The three patients with positive intradermal reactions to whom the desensitization protocol was administered developed delayed local reactions.

Systemic reactions (Table IV). Among the 13 cases with previous systemic reactions, the study was immediately positive in one both in the prick and in the intradermal test, and two cases developed delayed positivity. Thus, 15% of the prick tests were positive (one immediately and one delayed), and 23% of the intradermal tests were positive, in two cases after 24 hours. Out of these three patients with positive study, two refused desensitization and one developed generalised pruritus and coughing during it, without skin lesions or haemodynamic instability. All patients with negative studies tolerated the subcutaneous re-exposure.

DISCUSSION

Adverse reactions to tetanus toxoid have been associated to various factors: number of administration schedules, dose and route, and presence of adjuvants in the preparation (merthiolate, aluminium hydroxide). Several studies have reported a direct correlation between the levels of TT IgG

Table IV. Patient characteristics and study results in the cases with previous systemic reactions

Case No.	Gender	Age (years)	Symptoms	Latency	Elapsed time (years)	Serology (UI/ml)	TT prick	TT intradermal	Tolerance/desensitization
1	F	33	Urticaria + local	> 24 hours	2	N.P.	+ Delayed	+ Delayed	Immediate reaction
2	F	65	Exanthema	Hours	10	0,69	Negative	Negative	Yes
3	M	40	Urticaria	Hours	0,5	1,26	+ Immediate	+ Immediate	N.P.
4	F	63	Urticaria	Immediate	33	0,28	Negative	Negative	Yes
5	M	42	Exanthema	?	1	0,88	Negative	Negative	Yes
6	M	33	Urticaria	Hours	25	Negative	Negative	Negative	Yes
7	F	33	Dyspnoea	> 24 hours	0,5	0,112	Negative	Negative	Yes
8	F	63	Urticaria	> 24 hours	43	Negative	Negative	Negative	Yes
9	M	34	Urticaria	?	28	N.P.	Negative	Negative	Yes
10	F	62	Urticaria	Immediate	27	N.P.	Negative	Negative	Yes
11	F	53	Exanthema + local	> 24 hours	10	Negative	Negative	+ Delayed	N.P.
12	F	3/4	Exanthema	> 24 hours	0,4	N.P.	Negative	Negative	Yes
13	M	7	Urticaria	?	7	1,87	Negative	Negative	Yes

Abbreviations as in Table III.

antibodies and the severity of the local reaction^{6,7}. The pathogenesis of these reactions is considered to involve a type III immunologic reaction (Arthus' phenomenon) beginning after 2-8 hours, with deposition of circulating antibodies together with the local toxoid leading to an inflammatory response. In the present study, most patients evidenced protective titres of TT antibodies (83% in the local and 66% in the systemic reaction groups). In all the cases with negative serology, over two years had elapsed between the adverse reaction and the study (over ten years in most cases). In the patients studied less than two years after the adverse reaction protective titres were found in all the cases in which serology studies were performed. Some authors recommend that TT serology be carried out prior to the booster doses, in order to prevent unnecessary immunisations and avoid the risk of adverse reactions⁸.

A second possibility in the pathogenesis of the local reactions would be a delayed hypersensitivity (type IV) reaction induced by the presence of merthiolate in the preparation. In the patients here presented, the study of merthiolate hypersensitivity was negative in all cases, both in the epicutaneous and in the intradermal skin tests.

A type I (IgE-mediated) immunologic response has also suggested to be involved in anaphylactic reactions^{8,9} and in immediate local reactions¹⁰. The role of specific IgE antibodies to tetanus toxoid is open to debate, as detectable titres have been observed in immunised healthy subjects: in one

study they were detected in 10/32 persons (mainly in atopics)¹¹, and in another one in 25% of the cases, particularly in the first week after administration¹². No determinations of specific serum TT IgE antibodies were performed in the present study, so that an assessment of their diagnostic yield is not possible.

When the epidemiological features of the two groups with local and systemic adverse reactions are examined, some important differences are observed: a clear predominance of the female gender, an older age and a shorter time elapsed up to the study in the local reaction group. Atopy does not seem to be an important factor in either group. In both groups, the reactions were more frequently delayed, occurring after 2-4 hours after administration of the TT (in 70% of the local reaction and in 73% of the systemic reaction cases).

As for the diagnostic yield of the study, the skin tests were positive in 73% of the local reaction cases (11/15), as compared to only 23% in the systemic ones (3/13). The delayed reading 24 hours after the test in the prick and intradermal skin tests prior to subcutaneous administration is important because of the great frequency of late positive results, particularly in the local reaction cases (6/11, 54.6%). In the cases with systemic reaction, the skin tests have a high negative predictive value, as all cases tolerated re-exposure.

Desensitization has proved effective and has induced tolerance in type I adverse drug reactions

(for instance, with penicillin and insulin). Desensitization was performed in only three of the six cases previous local reaction and positive delayed tests, and induced multiple delayed local reactions at all points of subcutaneous administration. It therefore seems not to be useful in the case of delayed local reactions. The eventual results of desensitization cannot be assessed in the other cases, as it was not performed for a variety of reasons: presence of protective antibody titres (or pending results), or refusal on the side of the patients. In one case of previous systemic reaction, pruritus and coughing not associated to skin lesions or haemodynamic instability developed immediately after the first subcutaneous dose; this was difficult to interpret, as the patient had evidenced a local and systemic delayed reaction and the skin tests had been late positive.

The variability in the pathogenetic mechanisms of adverse reactions to tetanus toxoid give rise to varying patterns of results in the skin prick tests and to varying responses to the desensitization protocol.

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