ANTIBODY RESPONSE TO BOOSTER DOSE OF DIPHTHERIA AND TETANUS TOXOIDS

Reactions in Institutionalized Adults and Non-institutionalized Children and Young Adults

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FROM 1943 to 1950, large groups of institutionalized mentally ill or retarded patients and noninstitutionalized young adults and children were inoculated with different combinations of diphtheria and tetanus toxoids, pertussis and typhoid vaccines, and scarlet fever toxin. Studies, reported by Volk and associates (*1–4*), were made to determine the antibody responses and the reactions elicited by different dosages and combinations of these antigens. When a reinoculation study of certain of these groups was initiated in 1956, the first problem to be resolved was the efficacy of booster doses consistent with freedom from reactions.

This report deals with the studies which led to the selection of a 0.2-ml. booster dose, and therefore is a report of the reactions elicited by different doses of DT, diphtheria and tetanus toxoids, aluminum phosphate adsorbed, and DTP, diphtheria and tetanus toxoids, aluminum phosphate adsorbed, combined with pertussis vaccine.

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Methods

The 665 subjects in the studies were divided into 6 groups. Groups A, B, and C were adults in a hospital for the mentally ill, and groups D and E were residents of an institution for the mentally retarded; group F consisted of noninstitutionalized normal children and young adults (see table).

A registered nurse (M.G.G.) from the Saginaw County Health Department, who had observed all the reactions in previous studies, evaluated these reactions by using the criteria described earlier (*1*). For 11 days after the booster dose, the subjects were examined for evidence of local or general reactions. Reactions were recorded as mild: slight redness but no discomfort at site of injection; moderate: pronounced redness and some induration; and severe: pain, evident discomfort, and extensive swelling or induration. Severe local reactions usually were accompanied by mild systemic reactions. There were 80 noninstitutionalized subjects in group F in whom the site of injection was not observed but who were interviewed by telephone (*5*). Since these were teenagers and young adults, information on

the freedom from serious reactions was considered reliable. No "antigen cysts" were observed (*4*).

Prior to the earlier studies conducted in 1943–50 at both the Pontiac State Hospital (groups A, B, and C) and the Coldwater State Home and Training School (groups D and E), both diphtheria and typhoid antigens were administered, but not pertussis vaccine or tetanus toxoid. After 1950 the Pontiac State Hospital subjects were given Schick tests annually and, when indicated, a diphtheria toxoid booster. In addition, all subjects were given two or more injections of tetanus toxoid. The Coldwater State Home and Training School subjects were given injections of diphtheria and tetanus toxoids annually, beginning in 1956. The noninstitutionalized subjects (group F) had not received injections of antigens after their primary series. In general, then, the

Reactions in six groups after booster injections containing various multiple antigen preparations, expressed as percentages

Reactions	1st day	2d day	3d day	4th day	5th day	6th day	7th day	8th–11th day
	Institutionalized							
Pontiac State Hospital								
Group A (305 subjects, 0.2 ml. DTP):								
None	2	8	15	27	49	70	87	92
Mild	22	20	30	33	34	23	11	7
Moderate	30	22	29	30	13	5	1	1
Severe	46	50	26	10	4	2	1	0
Group B (79 subjects, 0.2 ml. DT):								
None	48	67	80	91	99	100	100	100
Mild	35	20	13	7	1	0	0	0
Moderate	11	8	6	2	0	0	0	0
Severe	6	5	1	0	0	0	0	0
Group C (76 subjects, 0.4 ml. DT):								
None	27	32	53	70	80	81	84	85
Mild	34	24	21	11	9	11	9	8
Moderate	25	14	8	8	4	7	7	7
Severe	14	30	18	11	7	1	0	0
Coldwater Hospital								
Group D (58 subjects, 0.2 ml. DT):								
None	76	79	95	98	100	100	100	100
Mild	24	21	5	2	0	0	0	0
Moderate	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0
Group E (53 subjects, 0.5 ml. DT):								
None	22	11	19	40	64	100	100	100
Mild	19	30	34	34	36	0	0	0
Moderate	34	25	21	26	0	0	0	0
Severe	25	34	26	0	0	0	0	0
	Noninstitutionalized							
Group F (94 subjects, 0.2 ml. DT):								
None	87	65	86	97	99	100	100	100
Mild	13	35	14	3	1	0	0	0
Moderate	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0

institutionalized subjects could be considered more likely to exhibit local or general reactions than the noninstitutionalized subjects (*4*).

The antigens were routine products of the division of laboratories, Michigan Department of Health. The DTP preparation contained 20 Lf (limes flocculation) units of diphtheria toxoid, 10 Lf units of tetanus toxoid, 24 opacity units of pertussis vaccine, and 0.56 mg. of aluminum (in the form of aluminum phosphate) per milliliter. The purity of the diphtheria toxoid was 1,490 Lf units, and the tetanus toxoid, 1,508 Lf units per milligram of protein nitrogen.

Antigenicity tests of the combined products were performed according to the minimum requirements of the National Institutes of Health. When the DTP was injected into guinea pigs, each human dose of 0.5 ml. produced 5 units of diphtheria and 6 units of tetanus antitoxin per milliliter of serum. Antigenicity tests on the pertussis component indicated that the DTP had a potency of 8.4 mouse protective units per milliliter.

The DT preparation contained 10 Lf units of diphtheria toxoid, 10 Lf units of tetanus toxoid, and 1.17 mg. of aluminum (in the form of aluminum phosphate) per milliliter. The purity of the diphtheria toxoid was 1,648 Lf units, and the tetanus toxoid, 1,603 Lf units per milligram of protein nitrogen. When the DT was injected into guinea pigs, each human dose of 0.5 ml. produced 2 units of diphtheria antitoxin and 4 units of tetanus antitoxin per milliliter of serum.

Results

As shown in the table, 305 subjects in one institution (group A) received 0.2 ml. of the DTP preparation; in 46 percent the reactions were severe and in 30 percent they were moderate. Group B, 79 subjects, received 0.2 ml. of the DT preparation. The frequency and severity of local reactions were greatly reduced (severe, 6 percent; moderate, 11 percent). To determine the effect of the size of the dose as a factor in causing reactions, a comparable group of 76 subjects (group C) in the same institution were given double the dose of the DT preparation, 0.4 ml. The severity and frequency of reactions were markedly increased (severe, 30 percent; moderate, 25 percent), although these reactions generally were not as severe as those after the booster injection of the DTP preparation.

Group D, 58 young institutionalized adults in the Coldwater State Home and Training School, were given 0.2 ml. of the DT preparation, and no moderate or severe reactions were observed. Group E, comparable to group D, in the same institution received a 0.5-ml. dose of the same DT preparation; the reactions were sharply increased in both the severe (25 percent) and moderate (34 percent) categories.

Of the 174 subjects in group F, 94 were observed by the nurse and are reported here; 80 were interviewed by telephone. Each received a DT dose of 0.2 ml. No moderate or severe reactions occurred.

Discussion

Two observations may be made from these data.

First, when the two comparable groups B and C received different doses of the same preparation, the reactions were more prominent and of longer duration in the group receiving 0.4 ml. DT than in the group which received 0.2 ml. DT.

The same observation was made in the younger comparable groups D and E. The subjects who received 0.2 ml. of the DT booster were relatively free from reactions compared with those who received the 0.5-ml. booster. The higher dose resulted in frequent moderate and severe local reactions.

The dose of 0.2 ml. contained 2 Lf units of diphtheria toxoid. This amount is within the limits of 1 to 5 Lf units which Edsall, Altman, and Gaspar (*6*) and Edsall, Banton, and Wheeler (*7*) suggested as the dose that could be used for booster inoculations without the risk of evoking too many severe reactions.

Wishart and Reid (*8*) found that 1 or 2 Lf units of fluid diphtheria toxoid injected subcutaneously into immunized young adults produced local reactions in as many as a third of the individuals injected, and moderate general reaction in 2 percent of the individuals of this age. Their product was not as pure and might

be more likely to cause reactions than the partially purified products used by the Massachusetts group (*6*, *7*, *9*) and by us.

There is also evidence that tetanus toxoid may be more often associated with reactions than was previously recognized. Levine, Ipsen, and McComb (*9*) injected an unadsorbed mixture of 1 Lf unit of diphtheria toxoid and 5 Lf units of tetanus toxoid. They found that some previously immunized persons reacted to the tetanus component, but they could not demonstrate that decreasing the tetanus toxoid component from 5 Lf units to 1 reduced the number of reactions; it did, however, lessen the severity of the reaction. Later McComb and Levine (*10*) recommended a subcutaneous booster dose, for adults, of a combined fluid product containing 1 Lf unit each of diphtheria and tetanus toxoids.

The 0.2-ml. dose we found satisfactory from the standpoint of evoking few reactions therefore was approximately equivalent in composition to that recommended by others. Our preparation differed, however, in being an aluminum phosphate adsorbed antigen and was administered intramuscularly.

The second observation is that when two groups received the same dose but different antigens, the preparation which contained diphtheria, tetanus, and pertussis antigens produced more frequent and severe reactions than the preparation containing only the diphtheria and tetanus antigens.

Because the three groups at the Pontiac State Hospital were comparable from the standpoint of prior immunization experience, age, and environment, we concluded that the pertussis antigen, when given to adults, was primarily responsible for the greater proportion of reactions observed in group A.

Summary

Both the frequency and the severity of reactions were studied in noninstitutionalized young adults and in institutionalized adults after injections of purified diphtheria and tetanus toxoids (10 Lf units each per milliliter), aluminum phosphate absorbed. Another group of institutionalized adults received diphtheria toxoid (20 Lf units per milliliter) and tetanus toxoid (10 Lf units per milliliter), aluminum phosphate adsorbed, combined with pertussis vaccine (24 opacity units per milliliter). Reactions to the antigens and doses decreased in frequency and severity in the following descending order: 0.2 ml. DTP, 0.5 ml. DT, 0.4 ml. DT, and 0.2 ml. DT.

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