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Clinical and Serological Evaluation of a Meningococcal Polysaccharide Vaccine Groups A, C, and Y (39995)

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Highly purified capsular polysaccharide vaccines prepared against groups A, C, and Y *Neisseria meningitidis* have been developed (1–3). These vaccines have been shown to be antigenic and free of significant side effects (3–6). Subsequently, group A, group C, and group A/C combined vaccines have been licensed for limited distribution and use by the Bureau of Biologics, Food and Drug Administration.

In order to broaden the potential protection afforded by a meningococcal vaccine, the group Y polysaccharide component was added to groups A and C polysaccharides. The purpose of this study was to evaluate such a combination vaccine with respect to clinical acceptability and serological response.

Materials and methods. Vaccines. The vaccine used in this study (Lot 2501) was prepared in the Merrell-National Research Laboratories using *Neisseria meningitidis* A-1, C-11, and 6306 Y (Slaterus Y) obtained from the Walter Reed Army Institute of Research. The cold phenol method of Gotschlich *et al.* (7) was used to purify the polysaccharides. Molecular sizing of the polysacchardies using Sepharose 4B gel permeation chromatography suggested that the three components of the vaccine were of high molecular weight. The partition coefficients (*Kd*) at the Ve were 0.26, 0.22, and 0.01, respectively, for the A, C, and Y polysaccharides. The individual polysaccharide components, A, C, and Y, were tested for pyrogenicity (three rabbits each component) at 0.25 μg/kg. The mean temperature rises were 0.2, 0.2, and 0.0° for the three components, respectively. The final vaccine was tested in eight rabbits at a concentration of 0.075 μg/kg (0.025 μg each component) with an average rise of 0.39°. These results are within limits established for meningococcal vaccines (8, 9). In addition, the vaccine met the general requirements of the Bureau of Biologics, Food and Drug Administration (8), and other existing standards pertinent to the use of vaccines (9).

A placebo consisting of isotonic sodium chloride with 0.01% thimerosal was used in this study.

Clinical studies. The study population consisted of healthy adult volunteers, employees and staff of a university hospital, who had given their informed consent. Both men and women, 18 to 57 years of age (mean age, 25.4 years), were included in the study population. The vaccine was administered to 30 individuals, each of whom received 0.5 ml (containing 50 μg of each of the three polysaccharides) subcutaneously, in the upper arm in the region of the deltoid muscle. Twenty-three of these individuals had not been immunized with a meningococcal vaccine. Of the other seven individuals, four had been immunized with a group A/C combined vaccine, two had received groups A and C vaccines, and one had been given a group C vaccine. All previous immunizations had been with 50 μg each of the respective polysaccharides. Five individuals received 0.5 ml of the placebo.

Blood specimens were obtained by venipuncture (antecubital vein) prior to immunization and 3 weeks later. Sera were collected and stored frozen at −20° until serological testing was conducted.

Clinical observations were made and recorded for each individual at 4-hr intervals

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until bedtime on the day of immunization, then daily for the next 3 weeks. Oral temperatures were taken for the first 3 days regularly, and continued if the volunteer had any symptoms. Any adverse local or systemic reactions were recorded on individual case report forms.

Bactericidal tests were performed on pre- and postimmunization sera (inactivated at 56° for 30 min) using a procedure developed by the Bureau of Biologics (8).

Results. Of the 30 individuals who received the vaccine, 12 reported symptoms of a systemic nature. Temperatures above 37.2° were observed in 6 individuals. In 5 of these 6 volunteers maximum temperatures ranged from 37.3 to 38.8°. Other temperature readings and symptoms further suggested a mild systemic reaction to the vaccine. Other symptoms of these 5 individuals were recorded on days postimmunization as follows: 1 individual, Day 1; 1 individual, Days 1 and 2; 2 individuals, Days 2 and 3; and 1 individual, Day 3. The sixth individual was reported to have had a temperature of 39.4° four hours after immunization, however, no other temperatures were abnormal and no other adverse reactions were observed. Complaints recorded for all 12 individuals above were headache (six instances), coryza (three instances), lethargy (three instances), nausea (three instances), and chills (one instance). All symptoms dissipated by Day 3.

Twenty-three of the 30 vaccinees (one of five placebos) complained of local pain or soreness at the site of injection, with the discomfort lasting 1 day for 12 individuals, 2 days for 4 individuals, and 3 days for 7 individuals.

No correlation was noted between symptoms observed and prior immunization with meningococcal vaccines.

Results of bactericidal antibody tests (Table I) of the sera from the 23 individuals not previously immunized with a meningococcal vaccine indicated that 23 (100%), 21 (91.3%), and 20 (87.0%) had significant (fourfold or greater) increases in group A, group C, and group Y antibodies. If individuals with high preexisting antibody levels are excluded, 95% or more of the individuals developed significant antibody levels to all three vaccine components.

The serological responses of seven individuals, after receiving the ACY vaccine, who had received meningococcal vaccine A, C, or A/C, are shown in Table II. All individuals developed high levels of group Y bactericidal antibodies. One individual who had previously received group C vaccine responded to the group A and group Y polysaccharides. Four of six individuals had serological rises of group A antibodies after their second contact with this polysaccharide. None of the seven individuals had any rises to group C antibodies, suggesting no booster effect with this particular polysaccharide.

Discussion. This study indicates that the

TABLE I. SERUM BACTERICIDAL ANTIBODY RESPONSES IN HUMAN SUBJECTS[a] MEASURED 3 WEEKS AFTER A SINGLE DOSE OF MENINGOCOCCAL POLYSACCHARIDE VACCINE, GROUPS A, C, Y.[b]

	Initial seronegatives			Initial seropositives		
Vaccine component	≧4 × Rise, No./total[c]	%	GM[d]	≧4 × Rise, No./total	%	GM
			<4			45
Group A	22/22	100	226	1/1	100	181
			<4			20
Group C	21/22	95	99	0/1	0	20
			<4			333
Group Y	19/20	95	333	1/3	33	1024

[a] Twenty-three individuals, no previous meningococcal vaccines.
[b] Fifty micrograms of each polysaccharide.
[c] Number showing rise/total number tested.
[d] Geometric mean titer.

TABLE II. RESPONSE OF VACCINEES TO GROUPS A. C, Y MENINGOCOCCAL VACCINE BY INDIVIDUALS PREVIOUSLY IMMUNIZED WITH GROUPS A AND/OR C VACCINES.

Individual	Previous meningococcal vaccine[a]/response[b]	Interval (months) before ACY vaccine	Response to ACY components[b]		
			A	C	Y
1	C+	26	+	−	+
2	A−, C+	27	+	−	+
3	A+, C+	27	+	−	+
4	A+/C+	13	−	−	+
5	A+/C+	31	+	−	+
6	A−/C−	19	−	−	+
7	A+/C+	19	+	−	+

[a] A, C, A/C denotes group A, group C, groups A/C combined meningococcal vaccines.
[b] Response + = fourfold or greater rise in bactericidal antibody.

groups A, C, and Y polysaccharide vaccine, while causing some mild reactions, is safe and clinically acceptable.

The serological conversions induced as a result of the immunization are of particular interest. A high percentage of those individuals with no prior experience with menigococcal vaccines developed significant levels of bactericidal antibodies to all three components of the vaccine. This suggests an independent immune response to each polysaccharide. The mean antibody level to the group Y polysaccharide component was not different from that observed with monovalent group Y vaccines, 333 versus 359 (3). In another clinical study in our laboratory with group C vaccine, the mean bactericidal antibody titer was 85, which was not different from the mean group C antibody titer observed in this study. In a separate clinical study with a new group A vaccine, the mean bactericidal antibody level was 188. Other clinical studies with A/C combined vaccine resulted in mean bactericidal antibody levels to the group A component of 695 and to the group C component of 488.

Further evidence of the independent response to meningococcal polysaccharide was the observation that individuals with prior experience with group A and group C polysaccharides developed bactericidal antibodies to the group Y component of the ACY vaccine.

A suggestion of a booster effect was observed with the group A component, but not the group C component of the ACY vaccine. A correlation has been made between the presence of bactericidal antibodies and resistance to meningococcal disease (10). Since clinical efficacy has been shown with polysaccharide vaccines of group A and C meningococci (4–6) which induce antibody levels comparable to those observed in this study, it seems probable that the groups ACY polysaccharide vaccine would be clinically efficacious.

Summary. The clinical and serological testing of a groups A, C, and Y meningococcal polysaccharide vaccine is described. Some minor reactions were observed. High levels of bactericidal antibody to all three components were observed in 90% of the individuals 3 weeks after receiving the vaccine.

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