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Immunogenicity of Vi Capsular Polysaccharide Vaccine Evaluated for Three Years in Korea

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The immunogenicity of a single dose of Salmonella typhi(S.typhi) Vi capsular polysaccharide(CPS) vaccine was evaluated before, and at 1, 3, 12, and 36 months after vaccination. Eighty-five adults(20-28 years of age) and sixty-four children(8-16 years of age) received a single dose of 25 μg Vi CPS vaccine intramuscularly, and antibody titers to Vi CPS were measured by passive hemagglutination. Of 149 vaccinees, 138(92.6 %) showed seroconversion at 1 month after vaccination, and then 138 out of 141(97.9 %) did at 3 months. Of 137 vaccinees, 116(84.7 %) maintained a persistent rise in Vi antibody titer 12 months after vaccination, and 55 out of 100(55.0 %) had a 4-fold or greater rise at 36 months. No significant adverse reactions were observed. Booster injection may be needed 3-5 years after vaccination.

Key Words : *Vi CPS vaccine, Typhoid fever, Immunogenicity*

INTRODUCTION

Typhoid fever caught by visitors who travel to endemic areas is a problem faced by developed countries. It is also one of the main public health problems faced by developing countries. Because of limitations in prevention through improvement of water supply and environment hygiene, vaccination is an important means to control typhoid fever. Inactivated whole-cell vaccine had weak points such as systemic side effects and required two doses(Ashcroft et al., 1967). Oral, live attenuated vaccine of *S.typhi* Ty21a strain has fewer side effects than inactivated whole-cell vaccine, but requires four doses on alternative days and should be refrigerated until it is taken(Kaplan and Hill, 1992).

Landy(1957) described that the Vi antigen of *S.typhi*, linked to the capsule of the bacterium, induces protective immunity in mice against a lethal intraperitoneal challenge injection of *S.typhi*. It is also capable of inducing a long lasting antibody response in humans(Landy et al., 1954). However, early attempts to vaccinate with purified Vi antigen were unsuccessful because the antigen had been denatured during extraction and purification(Martin et al., 1967). Later, new methods of preparation resulted in a more immunogenic product(Wong et al., 1974), and two large field trials have been done(Acharya et al., 1987 ; Klugman et al., 1987). There have been two reports about the follow-up of Vi antibody titers longer than 24 months in non-endemic areas(Tacket et al., 1988 ; Keitel et al., 1994). We examined the immunogenicity of a single dose of 25 μg Vi CPS vaccine for 3 years and evaluated the safety of the vaccine in Korea where typhoid fever is endemic.

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MATERIALS AND METHODS

Vaccine

The vaccines were supplied by the Institut Merieux, Lyon, France. Vi antigen was purified from *S.typhi* strain Ty-2, inactivated with formalin, and precipitated with hexadecyltrimethylammonium bromide. Vaccines contain 25 μg Vi antigen in 0.5 ml doses.

Study design

The subjects were 85 adults(20-28 years of age) and 64 children(8-16 years of age) who had not suffered from typhoid fever and had not been vaccinated against typhoid fever in the previous 10 years. We excluded pregnant women and persons who had been taken ill with acute or chronic disease, and had been vaccinated against other diseases in the previous 10 days.

A single dose of 25 μg Vi CPS vaccine was injected at the deltoid muscle, and blood samples were taken before, and at 1, 3, 12, and 36 months after vaccination. Antibody titer was measured by passive hemagglutination. When vaccinees had a 4-fold or greater rise in the antibody titer compared with the pre-vaccination titer, we regarded it as seroconversion.

Adverse reactions

Systemic reactions were defined as malaise, shivers, and itching. Localized reactions were classified as local pain, induration, and redness at the injection site. Vaccinees were asked if systemic reactions had taken place, and the injection sites were examined during the first 3 days after vaccination.

Statistical analysis

The changes in geometric mean antibody titers were examined by Scheffe's multiple comparison test, and those of the seroconversion rates were compared by chi squared test. P value of less than 0.05 was regarded as statistically significant.

RESULTS

Adverse reactions

Of 149 vaccinees, 80 had local pain at the injection site on the day of vaccination. Twenty-eight vaccinees had induration, and 6 had redness. For systemic reactions, 13 out of 149 vaccinees complained of malaise, and 1 experienced shivers(Table 1). But the reactions decreased within several days without any problems, and no one required bed rest.

Serologic responses(Table 2 and 3)

The combined geometric mean titer(GMT) before vaccination came out to be 4.3 in both groups. The titer of the adult group was greater than that of the children's group, 6.6 and 2.4 respectively.

One month after vaccination, seroconversion was observed in 138 out of 149 vaccinees(92.6 %). In the children's group, seroconversion rate(98.4 %) was greater than that of the adult group(88.2 %). The GMT increased markedly by 17 fold, and the antibody titers were similar in the two groups.

Three months after vaccination, in the adult group, 7 vaccinees who had been seroconverted at 1 month after vaccination dropped out of the study, but then 7 more vaccinees became seroconverted. Hence the seroconversion rate became 96.2 %. In the children's group, 1 recipient who had been seroconverted dropped out, but then 1 more vaccinee became

Table 1. Adverse reactions after Vi CPS vaccination.

	Day 0	Day 1	Day 2	Day 3
Localized reactions				
local pain	80/149(53.7%)	59/149(39.6%)	38/149(25.5%)	22/149(14.8%)
induration	28/149(18.8%)	22/149(14.8%)	12/149(8.1%)	4/149(2.7%)
redness	8/149(5.4%)	19/149(12.8%)	13/149(8.7%)	2/149(1.3%)
Systemic reactions				
malaise	13/149(8.7%)	6/149(4.0%)	3/149(2.0%)	1/149(0.7%)
shiver	1/149(0.7%)	0/149(0.0%)	0/149(0.0%)	0/149(0.0%)
itching	0/149(0.0%)	0/149(0.0%)	0/149(0.0%)	1/149(0.7%)

Table 2. Geometric mean titer(GMT) of serum Vi antibody.

	Before	1 Month	3 Months	12 Months	36 Months
Adults	6.6	79.1*	120.3*	41.7*	28.3*
Children	2.4	69.4*	49.2	36.7	7.2*
Combined	4.3	74.8*	80.6	39.6*	16.8*

*$p<0.05$, compared with previous GMT by Scheffe's multiple comparison.

Table 3. Seroconversion rate.

	1 Month	3 Months	12 Months	36 Months
Adults	75/85 (88.2%)	75/78 (96.2%)	61/81 (75.3%)*	35/62 (56.5%)*
Children	63/64 (98.4%)	63/63 (100.0%)	55/56 (98.2%)	20/38 (52.6%)*
Combined	138/149 (92.6%)	138/141 (97.9%)*	116/137 (84.7%)*	55/100 (55.0%)*

*$p<0.05$ compared with previous seroconversion rate by chi-squared test or Fisher's exact test.

seroconverted. So the seroconversion rate was 100 % at 3 months. The combined result at 3 months was a 97.9 % seroconversion rate in the test subjects. The GMT of the combined adult and children's group at 3 months was similar to that of the results at 1 month(80.6 at 3 months and 74.8 at 1 month). In the adult group, the GMT was 120.3, whereas in the children's group, it was 49.2. The individual titers of both groups were about 20 times their prevaccination titers.

Twelve months after vaccination, 61 out of 81 adults(75.3 %) maintained at least a 4-fold rise in Vi antibody titer compared to their prevaccination titer. In the children's group, 98.2 % of the vaccinees had a persistent rise in titer, compared with 75.3 % in the adult group. The GMT decreased in both groups.

Thirty-six months after vaccination, 55.0 % of the vaccinees had a persistent rise in titer compared with their prevaccination titer. In both groups, the percentages were similar. The combined GMT decreased even more than at 12 months. However, the absolute level was greater than that of the prevaccination titer.

DISCUSSION

The development of vaccine against typhoid fever can be classified into three steps. Inactivated whole-cell vaccine, that was developed first, should be administered initially two or three times with a one month interval, and then must be injected every year due to the short effective period. Morever, the lipopolysaccharide endotoxin, a contaminant in the vaccine caused systemic side effects(Hornick et al., 1970). The titers of Vi antibody produced after heat inactivated whole-cell vaccination were variable due to the degeneration of Vi antigen. Later, Vi antigenicity was well preserved in aceton-inactivated vaccine rather than heat-inactivated(Pittman and Hohner, 1966). The second, live attenuated vaccine from Ty 21a strain of salmonella had fewer side effects and made oral administration possible, but protective efficacy was variable in different localities(Wahdan et al., 1982 ; Levine et al., 1987). It should be stored in a refrigerator, and administered at two day intervals at least three times. These problems indicated the need for development of a new vaccine, that was easy to administer, and had persistent immunogenicity and fewer side effects.

Two large field trials have been done on Vi CPS vaccine against typhoid fever. Acharya et al.(1987) examined Vi CPS vaccine in 3,457 recipients in Nepal and followed up for 24 months resulting in 75 % protective efficacy. Klugman et al.(1987) vaccinated 11,384 schoolchildren in South Africa and followed up for 21 months resulting in 64 % protective efficacy. They measured Vi antibodies in a main trial before and at 6 and 12 months after vaccination in 29 children by radioimmunoassay and found that the antibody rise was sustained during the 12 months after vaccination.

There have been two reports about follow-ups of Vi antibody titers longer than 24 months in non-endemic areas. Tacket et al.(1988) followed 10 North American volunteers during 36 months. At first the number of their subjects was 24. At 21 months, 18 out of 19 subjects(95 %) maintained at least a 4-fold rise in antibody titer. At 36 months, 9 out of 10 subjects(90 %) had persistent rises in titer compared with their prevaccination titer. Their result shows some differences with our data(55 % at 36 months). Their subjects were from non-endemic areas, and small in number. In the study of Keitel et al.(1994), the mean Vi antibody levels remained significantly elevated for up to 34 months after primary immunization. This is concordant with our result that the GMT at 36 months was about 4 times the prevaccination titer. We observed differences in numbers of vaccinees who had persistent rises in antibody titers in the two groups at 12 months(75.3 % in the adult group and 98.2 % in the children's group), and in the rising folds of GMT compared with the prevaccination titers in two groups at 12 months. It was speculated that the serologic response of children's group which had lower prevaccination titer persisted longer than that of the adult group(Klugman et al., 1987).

In summary, this Vi CPS vaccine was relatively safe. At 36 months after vaccination, 55.0 % of the vaccinees had a persistent rise in titer compared to their prevaccination titer, but the absolute GMT was greater than that of the prevaccination titer. We think that more clinical study will be required, and booster injection may be needed 3-5 years after vaccination.

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