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Intradermal versus subcutaneous immunization with typhoid vaccine

By S. IWARSON

Department of Infectious Diseases, University of Göteborg, East Hospital, S-416 85 *Göteborg, Sweden*

AND P. LARSSON

Institute of Medical Microbiology, University of Göteborg, S-413 46 *Göteborg, Sweden*

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SUMMARY

Swedish nationals about to travel abroad were immunized against typhoid with a monovalent heat-inactivated vaccine which was administered intra- or subcutaneously. No major differences in serum antibody response were noted in the two groups of vaccinees as determined with direct agglutination and indirect hemagglutination techniques. As the intracutaneous route caused fewer adverse reactions this way of administration seems to be preferable.

INTRODUCTION

Already in the early thirties it was observed that intracutaneous immunization with one fifth of the normal dose of typhoid vaccine resulted in as much antibody response as subcutaneous immunization with the normal dose (Tuft, Yagle & Rogers, 1932). It was also found that the reaction to vaccination was lower after intracutaneous immunization. These observations have been confirmed in a series of studies during the forties and fifties as summed up by Clasener & Beunders (1967). On the other hand, some observers have come to different conclusions (Morgan, Favorite & Horneff, 1943; Luippold, 1944; Bardhan, Dutta & Krishnaswami, 1963).

In 1976 the previously used Swedish TAB-vaccine was changed into a monovalent typhoid vaccine. Since this type of heat-inactivated typhoid vaccine, in Sweden mainly used for foreign travellers, seemed to cause severe local or general reactions in about 75% of the vaccinees (Iwarson, 1977), a trial with intradermal administration of the vaccine was started.

MATERIALS AND METHODS

Subjects

A total of 78 Swedish nationals about to travel abroad, who were vaccinated at the Department of Infectious Diseases, Göteborg, Sweden, from November 1977 to September 1978, were divided into two groups, one of which received 0·5 ml of

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heat-inactivated typhoid vaccine subcutaneously (33 persons) and another group (45 persons) which was immunized with 0·1 ml of the same vaccine intracutaneously. Those vaccinated on a Monday or Wednesday received intracutaneous administration, while persons attending on Tuesdays got the vaccine subcutaneously. A second injection was given to most patients 2–4 weeks after the first injection but only 13 of them were followed with further antibody analyses since the majority of the travellers left shortly after the second injection.

Vaccine

The typhoid vaccine used was prepared by the State Bacteriological Laboratory (SBL), Stockholm, Sweden, by heat-inactivation of the typhoid organisms. Phenol (0·5 %) was added as preservative. One ml of the vaccine contained about 1000 million organisms. The vaccine was injected high up on the upper arm.

Serological methods

Antibodies to the *Salmonella typhi* O antigen were determined in serum samples for a check of the immunizations. Serum specimens were obtained before vaccination. In persons who were not leaving the country within 2 weeks, a second serum sample was taken 2–4 weeks after the primary injection. In the 13 who got a second injection (8 intradermal, 5 subcutaneous), a serum sample obtained 3–4 weeks after the second injection was tested. The sera were stored at −20 °C until tested.

Serum antibodies to the *S. typhi* O antigen were determined by direct bacterial agglutination (Widal) (Kauffmann, 1969). Antibodies were also measured with the indirect hemagglutination (IHA) technique (Neter, 1956; Jodal, 1975). Mercaptoethanol treatment to reveal IgG antibodies was performed as earlier described (Hanson *et al.* 1971). A Vi-negative *S. typhi* strain (NCTC 779) was used as antigen.

Statistical evaluations were performed using the chi-square test.

RESULTS

Clinical reactions

The reactions after the first immunization are shown in Table 1. Most of the vaccinees experienced local lesions at the site of inoculation high up on the upper arm. A severe reaction with a tender induration 5 cm in diameter or greater, surrounded by an erythematous zone, occurred in 34 vaccinees (severe local reaction according to Table 1). This type of severe local reaction was seen in 76 % after the first subcutaneous injection and in 20 % after intracutaneous administration, a significant difference ($P < 0{\cdot}001$). In nearly a third of these persons with severe local reactions, general reactions with nausea, malaise and fever were also seen but again with a significant difference between the subcutaneous group (33 % general reactions) and the intradermal group (4 %) ($P < 0{\cdot}001$). A moderate reaction defined as a tender induration less than 5 cm in diameter was seen in the majority of the intracutaneously injected individuals (Table 1). The clinical reactions after the second injection were not systematically studied.

Antibody determinations

Antibody values in sera obtained before immunization in the 78 patients are shown in Table 2. Most titre values (96%) were ⩽ 40 as determined with direct bacterial agglutination. With the indirect hemagglutination method 94% of the sera revealed titres ⩽ 64. Previous vaccinations with the old TAB vaccine were not associated with higher serum antibody titres as compared to unvaccinated controls (median titre values < 20 /Widal/, 16 /IHA/ for both groups).

Table 1. *Local and general reactions after intracutaneous* (0·1 *ml*) *and subcutaneous* (0·5 *ml*) *administration of heat-inactivated typhoid vaccine*

(In both instances the injection was given high up on the upper arm. The reactions to the first injection are reported.)

Administration of typhoid vaccine	No. of individuals studied	Local reaction			Local and general reaction with fever
		Severe	Moderate	None	
Subcutaneously (0·5 ml)	33	25* (75·8%)	8	0	11** (33·3%)
Intracutaneously (0·1 ml)	45	9* (20%)	21	15	2** (4·4%)

* $P < 0{\cdot}001$ ** $P < 0{\cdot}001$.

Table 2. *Pre-vaccination titres to* S. typhi *O antigen as determined with direct and indirect agglutination techniques*

Category	No. of individuals	Direct bacterial agglutination titres (Widal)				Indirect hemagglutination titres (IHA)					
		< 20	20	40	80	⩽4	8	16	32	64	⩾128
Previously vaccinated	58	35*	17	4	2	11	14	16	8	4	5
Unvaccinated	20	10	5	4	1	3	7	7	2	1	0
Total	78	45	22	8	3	14	21	23	10	5	5
%		57·7	28·2	10·3	3·8	18·0	26·9	29·5	12·8	6·4	6·4

* No of individuals.

The titres obtained after one injection were studied in 44 patients (16 subcutaneously and 28 intradermally injected). As a rule an increase in titre of at least two dilution steps was seen with both methods used (Widal and IHA). An antibody response was noted for most patients as is seen in Figs. 1(*a*, *b*) and 2(*a*, *b*).

The serum antibody response after two doses given 2–4 weeks apart was determined in 8 patients receiving intradermal injections and in 5 patients vaccinated subcutaneously. The antibody response after one and two injections, respectively, is shown in Fig. 3. As is seen from the figure the antibody titres 3–4 weeks after the second injection did not differ significantly from those seen about 3 weeks after the first injection (median titres 80 and 160, respectively).

Antibody titres after treating the sera with mercaptoethanol were greatly reduced as determined by the indirect hemagglutination method. Low antibody

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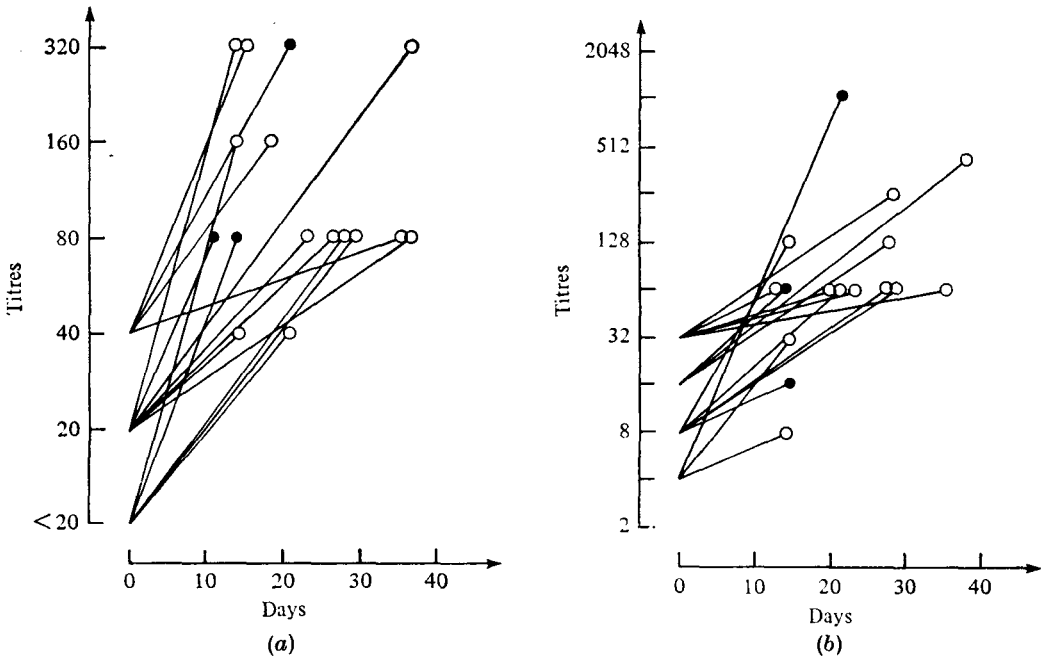

Fig. 1. Serum antibody titres as determined with (*a*) direct bacterial agglutination and (*b*) indirect hemagglutination after one subcutaneous dose of 0·5 ml *S. typhi* vaccine in unvaccinated (○) and previously TAB-vaccinated persons (●).

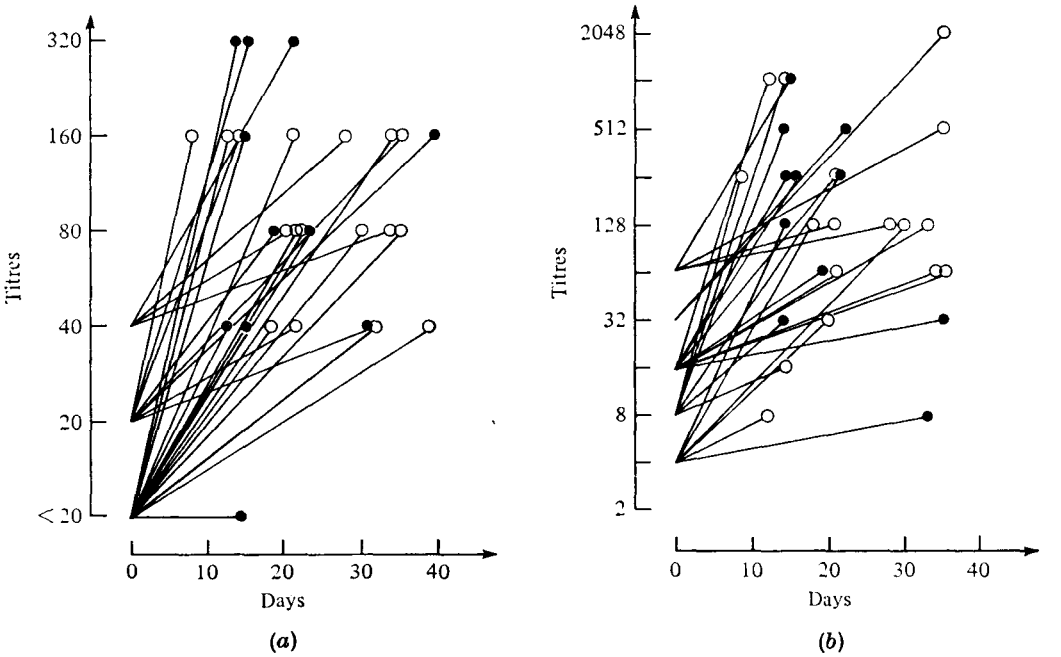

Fig. 2. Serum antibody titres as determined with (*a*) direct bacterial agglutination and (*b*) indirect hemagglutination after one intradermal dose of 0·1 ml *S. typhi* vaccine. Symbols as in Fig. 1.

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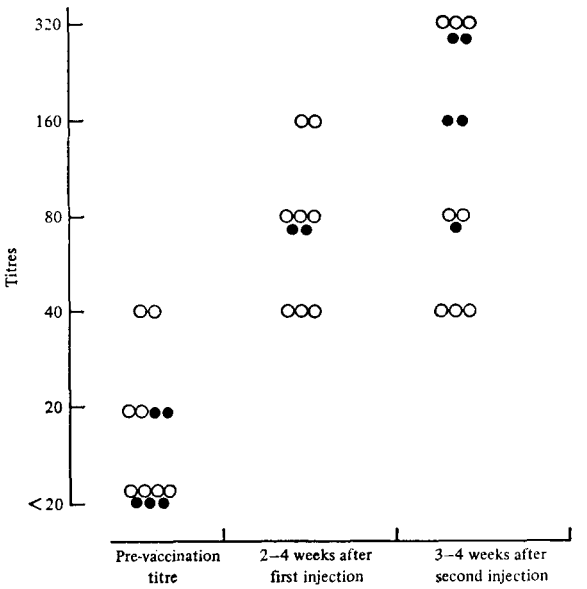

Fig. 3. Serum antibody titres as determined with direct bacterial agglutination in persons receiving two doses of *S. typhi* vaccine given intradermally (○) or subcutaneously (●).

titres ($\leqslant$ 16 in 93 % of sera tested) were noted after both one and two immunizations, indicating that the antibody response measured was mainly of the IgM class.

DISCUSSION

Severe local as well as generalized reactions with fever were more common among those who were vaccinated subcutaneously. Only 20 % of those who were intracutaneously vaccinated experienced a more severe local reaction on the site of vaccination, compared with about 76 % of the subcutaneously vaccinated persons. Two persons only experienced general reactions in the intracutaneous group compared with 11 in the other group. Other authors have also found that the smaller dose (0·1 ml) used for intradermal administration evokes fewer reactions than the larger dose (0·5 ml) given subcutaneously (Chiang & Ch'en, 1958; Hooper, 1964).

However, there have also been reports that intracutaneous vaccinations cause equally or more severe reactions than subcutuneous administration of the antigen (Bardhan *et al.* 1963; Zuckerman, 1964). The main reason for this seems to be that vaccines with different numbers of typhoid bacteria have been used (Bardhan *et al.* 1963; Hooper, 1964).

The function of a vaccine is to stimulate a protective immune response. In the present as well as in other studies (Luippold, 1944; Bardhan *et al.* 1963; Clasener & Beunders, 1967) the intracutaneous and subcutaneous routes of immunization have been shown to elicit a similar serum antibody response. Typhoid fever is, however, primarily an intestinal disease, the port of entry being in the gut. Thus mucosal defence mechanisms, mainly such as secretory IgA, might be of equal or greater importance than serum antibodies (Hanson & Brandtzaeg, 1979).

Field trials in over 175000 individuals carried out by Hejfec *et al.* (1968) showed that one intradermal injection of typhoid vaccine gave a protective effect up to one year. Two injections, however, had a protective effect of about 3 years. Thus, it seems that one intradermal injection of typhoid vaccine affords protection for short-term foreign travels as has been previously pointed out (Editorial, 1970).

Parenteral immunizations have been shown to boost a secretory IgA response against *V. choleroe* in areas where natural exposure was considered to be the primary antigenic stimulus (Svennerholm *et al.* 1977). If these data are valid also for *S. typhi* the protective effect of vaccination against typhoid ought to be related to the natural occurrence of *S. typhi* in the country studied. Thus, a low frequency of typhoid fever in the country of the vaccinee may call for more than one dose of typhoid vaccine at least to offer a more long-lasting protection.

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