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The effect of immune globulin on the response to trivalent oral poliovirus and yellow fever vaccinations

JONATHAN E. KAPLAN,[1] DAVID B. NELSON,[2] LAWRENCE B. SCHONBERGER,[3] MILFORD H. HATCH,[4] THOMAS P. MONATH,[5] JOHN S. LAZUICK,[6] CHARLES H. CALISHER,[7] & FRANZ W. ROSA[8]

To assess whether immune globulin may be administered concurrently with trivalent oral poliovirus vaccine (OPV) or yellow fever vaccine, antibody responses were studied in Peace Corps volunteers embarking for overseas duty in 1978. Of 200 volunteers who received OPV, 192 (96%) had pre-existing neutralizing antibody to at least 2 poliovirus types; of 160 yellow fever vaccinees, 24 (15%) had pre-existing 17D yellow fever antibody. Each volunteer received 5 ml of immune globulin, 0–7 days before, 3–5 days after, or 28–32 days after vaccination. This last group was designated the control group. Of the volunteers who received immune globulin 0–7 days before vaccination, 71% 72%, 49%, and 82% responded to poliovirus types 1, 2, and 3, and yellow fever, respectively (response was defined as a 4-fold or greater rise in serum neutralizing antibody titre between baseline (0–7 days before vaccination) and follow-up (15–40 days after vaccination)). These rates did not differ significantly from those in persons who received immune globulin 28–32 days after vaccination (61%, 60%, 51%, and 83%, respectively). Thus, among individuals who, for the most part, were immune to poliomyelitis but not to yellow fever, immune globulin did not decrease the antibody response to OPV or to yellow fever vaccine when given 0–7 days before vaccination.

Physicians are frequently confronted with people who are about to travel abroad and are in need of several vaccinations. A specific question concerns the concurrent administration of immune globulin (IG), which is used to prevent hepatitis A, and various live-virus vaccines. Although specific immune globulins are given in conjunction with inactivated vaccine products, such as those for tetanus and rabies, current recommendations dictate that IG should not be given within 3 months before, or until 2 weeks after, administration of a live, attenuated virus vaccine (*1*). The only data that support this recommendation, however, pertain to live, attenuated measles vaccine; the antibody response to this vaccine is diminished in persons who receive IG concurrently (*2*).

This study was undertaken to determine the effect of immune globulin on the response to trivalent oral poliovirus vaccine (OPV) and yellow fever vaccine—live-virus vaccines that are given to many international travellers.

METHODS

The study subjects were 201 Peace Corps volunteers who embarked for overseas duty in 1978. These volunteers were all healthy, and had a median age of 24 years (range, 20–70 years); 58% were male and 42% female. Each volunteer received a single dose of trivalent OPV and (with the exception of 34 persons bound for Tunisia, where yellow fever is not endemic) an intramuscular dose of 17D-strain yellow fever vaccine on the same day. Diphtheria, tetanus, typhoid, smallpox, and rabies vaccines were given to all volunteers and cholera vaccine was given to all except those bound for Honduras. Smallpox, cholera, and in some cases, typhoid vaccines were

[1] Medical Epidemiologist, Division of Viral Diseases, Centers for Disease Control (CDC), Atlanta, GA 30333, USA.

[2] Assistant Professor, Departments of Pediatrics and Preventive Medicine, Medical College of Wisconsin, Milwaukee, WI, USA.

[3] Chief, Epidemiology Office, Division of Viral Diseases, CDC, Atlanta, GA, USA.

[4] Chief, Enterovirus Laboratory, Respiratory and Enterovirus Branch, Division of Viral Diseases, CDC, Atlanta, GA, USA.

[5] Director, Division of Vector-Borne Viral Diseases, CDC, Fort Collins, CO, USA.

[6] Research Biologist, Arbovirus Reference Branch, Division of Vector-Borne Viral Diseases, CDC, Fort Collins, CO, USA.

[7] Chief, Arbovirus Reference Branch, Division of Vector-Borne Viral Diseases, CDC, Fort Collins, CO, USA.

[8] Epidemiologist, Epidemiology Development Branch, Division of Drug Experience, National Center for Drugs and Biologics, Rockville, MD, USA.

administered on the same day as OPV and yellow fever vaccine; the remaining vaccines, as well as additional doses of typhoid, cholera, and rabies vaccines, were given later, generally within 2 months of arrival in the country of destination. A 5-ml dose of commercially available immune globulin was administered intramuscularly to each volunteer, either 0–7 days before, 3–5 days after, or 28–32 days after vaccination. The last group of volunteers was designated the control group, since the major antibody responses to OPV and yellow fever vaccine almost always occur within 28 days of vaccination (*3*,*4*); hence, administration of IG at this late date should interfere relatively little, if at all, with the antibody response to these vaccines.

A baseline specimen of venous blood was obtained from each volunteer 0–7 days before vaccination, and follow-up specimens were obtained 15–40 days after vaccination. Samples were centrifuged, and the serum was separated and transported to the Centers for Disease Control, where it was stored at −70 °C, until tested.

Antibodies to poliovirus types 1, 2, and 3 were measured in the serum samples and in all five lots of IG that were available, using a microneutralization test (*5*). Samples were tested at 2-fold dilutions ranging from 1:10 to 1:1280. Antibodies to the 17D strain of yellow fever were determined by plaque-reduction neutralization (*6*). Specimens from 81 of 144 subjects (56%) with baseline yellow fever antibody titre $\leqslant$ 1:20 were tested in 1979 in 10-fold dilutions ranging from 1:2 to 1:200. Specimens from the remaining 63 subjects with baseline titre $\leqslant$ 1:20 were tested in 1982 in 4-fold dilutions ranging from 1:10 to 1:640. For the purposes of this study, an antibody response was defined as a 4-fold or greater rise in antibody titre (or, in subjects whose yellow fever antibody titres were measured in 10-fold dilutions, a 10-fold or greater rise in titre) between baseline (0–7 days before vaccination) and follow-up (15–40 days after vaccination).

The magnitude of the antibody response to each vaccine was assessed by determining the proportion of individuals with baseline antibody titres $\leqslant$ 1:20 (or, in the case of subjects whose yellow fever antibodies were measured in 4-fold dilutions, $\leqslant$ 1:10) who achieved a peak antibody titre $\geqslant$ 1:160 (or, in the case of subjects whose yellow fever antibodies were measured in 10-fold dilutions, $\geqslant$ 1:200).

RESULTS

Immune globulin

All 5 lots of immune globulin tested contained neutralizing antibody against all 3 types of poliovirus (titre $\geqslant$ 1:640 against types 1 and 2 in all 5 lots; $\geqslant$ 1:640 against type 3 in one lot, 1:320 in 4 lots). All 5 lots also contained antibody against the 17D strain of yellow fever at titres $\geqslant$ 1:640.

Poliovirus antibodies

A total of 200 subjects were analysed for poliovirus antibodies (one subject was excluded because the baseline serum specimen was lost). Of these, 163 (82%) had antibodies to all 3 poliovirus types. An additional 29 subjects (15%) had antibodies to 2 of the 3 poliovirus types (24 lacked detectable antibody to poliovirus type 3, 5 to type 1); 7 had antibody to only one poliovirus type. Only one subject was seronegative to all 3 types.

The percentages of volunteers responding to vaccination, by baseline antibody titre, are shown in Fig. 1. For each poliovirus type, the percentage of volunteers who responded decreased with increasing baseline antibody titre; this was true regardless of the time at which immune globulin was administered. Fewer volunteers responded to poliovirus type 3 than to types 1 and 2.

The data for all persons with baseline titres $\leqslant$ 1:80 are combined in Table 1. For each poliovirus type, the proportions of subjects with baseline antibody titre $\leqslant$ 1:20, 1:40, and 1:80 were similar in each comparison group (the proportion of subjects with a baseline titre $\leqslant$ 1:20 to poliovirus type 3 was higher than

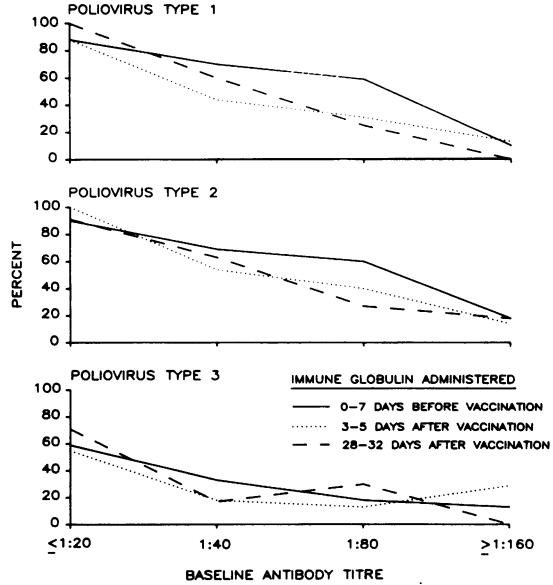

Fig. 1. Percentage of subjects responding to live, attenuated poliovirus vaccine, i.e., showing at least a 4-fold increase in neutralizing antibody titre.

Table 1. Percentage of subjects responding to live, attenuated virus vaccine[a] by time of administration of immune globulin

	Administration of immune globulin			Total
	0–7 days before vaccination (%)	3–5 days after vaccination (%)	28–32 days after vaccination (%)	
Poliovirus type 1	71 (59)[b]	50 (30)	61 (31)	63 (120)
Poliovirus type 2	72 (64)	52 (31)	60 (30)	64 (125)
Poliovirus type 3	49 (100)	36 (39)	51 (37)	47 (176)
Yellow fever vaccine (17D)	82 (98)	80 (10)	83 (36)	82 (144)

[a] Response defined as a 4-fold increase in neutralization antibody titre between baseline (0–7 days before vaccination) and follow-up (15–40 days after vaccination).

[b] Figure in parentheses indicates number of volunteers tested; only volunteers with baseline titres $\leqslant 1:80$ (poliovirus) and $\leqslant 1:20$ (yellow fever) are included.

those for types 1 and 2, but this proportion was similar in the three comparison groups). The antibody response rate among volunteers who received immune globulin 3–5 days after vaccination was consistently lower than that among those who received immune globulin 28–32 days after vaccination, but the difference was not statistically significant ($\chi^2 = 0.40$, 0.16, and 1.27 for the 3 poliovirus types, respectively; $P > 0.05$). However, there was no decrease in response among persons receiving immune globulin 0–7 days before vaccination, in comparison with the control group.

Among persons with a baseline antibody titre $\leqslant 1:20$, similar percentages in the three groups achieved peak antibody titres $\geqslant 1:160$ (Table 2).

Analysis of the antibody response rates in subjects who were initially seronegative showed nearly 100% seroconversion in all groups; the proportions of subjects with peak titres $\geqslant 1:160$ were similar to those in all volunteers with baseline titres $\leqslant 1:20$ (Tables 2 and 3). However, the numbers of subjects in these groups were small.

Analysis of poliovirus antibody response rates and peak antibody titres in those who did, and did not, receive yellow fever and cholera vaccines revealed one statistically significant difference: the antibody response rate to poliovirus type 1 in volunteers receiving cholera vaccine (57% of 88) was significantly lower than that in those not receiving cholera vaccine (81% of 32, $\chi^2 = 5.03$, $P < 0.05$). However, between those receiving and not receiving cholera vaccine, there was no significant difference in antibody response rates to poliovirus types 2 or 3 and no significant difference in the percentages of individuals with peak antibody titres $\geqslant 1:160$ to any of the poliovirus types.

Table 2. Percentage of subjects with peak neutralizing antibody titre $\geqslant 1:160$ following trivalent oral poliovirus and yellow fever vaccination

	Administration of immune globulin			Total
	0–7 days before vaccination (%)	3–5 days after vaccination (%)	28–32 days after vaccination (%)	
Poliovirus type 1	82 (17)[a]	63 (8)	75 (8)	76 (33)
Poliovirus type 2	76 (21)	67 (3)	73 (11)	74 (35)
Poliovirus type 3	37 (68)	35 (20)	33 (21)	36 (109)
Yellow fever vaccine (17D)	39 (97)	22 (9)	50 (36)	41 (142)

[a] Figure in parentheses indicates number of volunteers tested; only volunteers with baseline antibody titres $\leqslant 1:20$ are included.

Table 3. Poliovirus and yellow fever antibody response rates and percentages of peak neutralizing antibody titres ⩾ 1 : 160 among subjects who were initially seronegative[a]

	Administration of immune globulin							
	0–7 days before vaccination		3–5 days after vaccination		28–32 days after vaccination		Total	
	Response rate (%)	Titre ⩾ 1 : 160 (%)	Response rate (%)	Titre ⩾ 1 : 160 (%)	Response rate (%)	Titre ⩾ 1 : 160 (%)	Response rate (%)	Titre ⩾ 1 : 160 (%)
Poliovirus type 1	100 (6)	83 (6)	67 (3)	33 (3)	100 (2)	50 (2)	91 (11)	64 (11)
Poliovirus type 2	100 (1)	0 (1)	(0)	(0)	100 (2)	100 (2)	100 (3)	67 (3)
Poliovirus type 3	84 (19)	32 (19)	83 (6)	17 (6)	86 (7)	29 (7)	84 (32)	28 (32)
Yellow fever (17D)	82 (93)	37 (92)	78 (9)	25 (8)	82 (34)	50 (34)	82 (136)	40 (134)

[a] Figures in parentheses give number of subjects tested.

Yellow fever antibodies

A total of 160 volunteers were included in the analysis of yellow fever antibodies (serum specimens from 7 individuals were lost, and 34 individuals bound for Tunisia did not receive the vaccine). Of these, 136 (85%) had no detectable antibodies to yellow fever prior to the administration of vaccine. An additional 8 (5%) had detectable baseline antibody titres ⩽ 1 : 20. The antibody response rate among the 144 volunteers with baseline antibody titres ⩽ 1 : 20 was higher than that among those with baseline titre 1 : 40 or 1 : 160 (82% versus 20%, $P = 0.006$, Fisher exact test). Only individuals with baseline antibody titres ⩽ 1 : 20 are included in Table 1. Among these individuals, similar antibody response rates were observed in those who received immune globulin 0–7 days before, 3–5 days after, and 28–32 days after vaccination (Table 1). The percentage of volunteers who achieved a peak antibody titre ⩾ 1 : 160 (or ⩾ 1 : 200) was slightly lower among those who received immune globulin 0–7 days before vaccination than among the controls, but the difference was not statistically significant ($\chi^2 = 0.86$, $P > 0.05$, Table 2).

Analysis of antibody response rates and peak antibody titres did not suggest that administration of cholera vaccine interfered with the response to yellow fever vaccine: the antibody response rate was 82% in those receiving, and those not receiving, cholera vaccine, and the percentages of volunteers with peak titre ⩾ 1 : 160 were 44% and 37%, respectively.

We also analysed the data according to whether 10-fold or 4-fold dilutions had been used in the serological tests. Volunteers whose specimens were tested at 10-fold dilutions had a higher antibody response rate to yellow fever vaccine than those whose specimens were tested at 4-fold dilutions (86% of 81 versus 76% of 63), as well as a higher percentage with peak antibody titre ⩾ 1 : 160 (48% of 81 ⩾ 1 : 200 versus 31% of 61 ⩾ 1 : 160), but neither of these differences was statistically significant. Comparison of antibody response rates and percentages of volunteers with peak antibody titre ⩾ 1 : 160 (or ⩾ 1 : 200) between persons receiving immune globulin 0–7 days before vaccination and those receiving it 28–32 days after vaccination within each of these groups did not reveal any significant differences.

DISCUSSION

The Peace Corps volunteers in this study were essentially immune to poliomyelitis prior to the administration of OPV, and the results of the study are therefore most pertinent to individuals or populations who have such immunity. Volunteers initially seronegative (at a 1 : 10 level) to the various polioviruses had antibody response rates and peak titres that did not appear to vary with the time of IG administration (Table 3). This suggests that immune globulin does not interfere with the immune response to OPV in populations lacking detectable antibody to one or more poliovirus types, but the numbers of subjects included in the analyses were insufficient to allow firm conclusions to be drawn.

Our results indicate that, in individuals who have pre-existing immunity to polioviruses, administration of immune globulin concurrently with, or less than 7 days before, vaccination with OPV, does not significantly decrease the rate or the magnitude of the antibody response to this vaccine.

Unlike the situation as regards polioviruses, most volunteers in the study (85%) were seronegative to yellow fever virus before administration of vaccine;

hence the conclusions of this study are most pertinent to individuals or populations lacking antibody to yellow fever. Individuals who were initially seropositive but with titres $\leqslant 1:20$ (5% of the volunteers) had antibody response rates and peak antibody titres similar to those who were initially seronegative, but the relatively small numbers of such individuals suggest the need for caution in drawing any conclusions concerning this group.

Our findings suggest that administration of immune globulin concurrently with, or less than 7 days before, yellow fever vaccine, in a population that, for the most part, is susceptible to yellow fever, does not decrease the seroconversion rate or the magnitude of the antibody response to this vaccine. Concurrent administration of immune globulin and yellow fever vaccine, therefore, appears acceptable. Additionally, unlike other studies (*7*, *8*), our findings do not suggest that cholera vaccination interferes with the response to yellow fever vaccine.

The finding of significant titres of yellow fever antibody in all 5 lots of immune globulin tested indicates that these antibodies are commonly present in commercially available IG in the USA; to our knowledge, this finding has not been reported previously. Apparently, persons with elevated yellow fever antibody titres are included in the population donating plasma for use in IG preparation. Although we do not know who contributed to the immune globulin used in this study, it is possible that the donors include veterans from the Second World War and the Viet Nam war, and others who may have received yellow fever vaccine or even been exposed to yellow fever. Poland et al. (*9*) have reported that 65% of 149 veterans of the Second World War had detectable neutralizing antibody to the 17D strain of yellow fever, 30 years after the war; 31% had titres $\geqslant 1:64$, the highest dilution tested. Since plasma is concentrated roughly 20 times in the preparation of immune globulin (*10*), one donor with a yellow fever antibody titre of 1:640 per 20 plasma donors would be sufficient to confer an equivalent titre to the resultant lot of IG.

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RÉSUMÉ

L'EFFET DES IMMUNOGLOBULINES SUR LA RÉPONSE AU VACCIN ANTI-POLIOMYÉLITIQUE BUCCAL TRIVALENT ET AU VACCIN ANTIAMARIL

Afin de déterminer si des immuno globulines (IG) peuvent être administrées en même temps que du vaccin antipoliomyélitique buccal trivalent ou du vaccin antiamaril, on a étudié les réponses en anticorps chez des membres du Corps des Volontaires de la Paix (Peace Corps) qui allaient servir outre-mer en 1978. Sur les 200 volontaires qui ont reçu le vaccin antipoliomyélitique, 192 (96%) possédaient des anticorps neutralisants préexistants à l'égard de 2 types de poliovirus au moins; sur les 160 sujets vaccinés contre la fièvre jaune, 24 (15%) avaient un anticorps préexistant contre la souche de virus amaril 17D. Chaque volontaire a reçu 5ml d'IG soit 0 à 7 jours avant la vaccination, soit 3 à 5 jours après, soit 28 à 32 jours après. Ce dernier groupe constituait le groupe témoin. Chaque lot d'IG contenait des anticorps neutralisants contre les 3 types de poliovirus ($\geqslant 1:320$) et contre la fièvre jaune ($\geqslant 1:640$). La réponse à la vaccination était définie comme un quadruplement au moins du titre des anticorps neutralisants entre le sérum de référence (recueilli 0 à 7 jours avant la vaccination) et le sérum prélevé 15 à 40 jours après la vaccination. Seuls les volontaires dont les titres initiaux d'anticorps étaient inférieurs ou égaux à 1:80 à l'égard du poliovirus et à 1:20 à l'égard du virus amaril ont été inclus dans les analyses. Parmi les volontaires qui ont reçu l'IG 0 à 7 jours avant la vaccination, une réponse a été observée à l'égard du poliovirus des types 1, 2 et 3 ainsi que du virus amaril, respectivement, chez 71% (sur 59), 72% (sur 64), 49% (sur 100) et 82% (sur 98). Parmi les sujets qui ont reçu de l'IG 3 à 5 jours après la vaccination, une réponse a été notée chez 50% (sur 30), 52% (sur 31), 36% (sur 39) et 80% (sur 10). Ces taux ne diffèrent pas significativement de ceux qui ont été enregistrés chez les personnes ayant reçu l'IG 28 à 32 jours après la vaccination, à savoir 61% (sur 31), 60% (sur 30), 51% (sur 37) et 83% (sur 36). Pour chaque groupe témoin, parmi les volontaires dont les titres de référence des anticorps étaient inférieurs ou égaux à 1:20, on a également déterminé le pourcentage de sujets dont les anticorps ont atteint des titres supérieurs ou égaux à 1:160 après la vaccination. Chez les volontaires qui ont reçu l'IG 0 à 7 jours avant la vaccination, ces pourcentages ont été à l'égard du poliovirus des types 1, 2 et 3 et du virus amaril, respectivement, de 82% (sur 17), 76% (sur 21), 37% (sur 68), et 39% (sur 97). Dans le cas des sujets qui ont reçu l'IG 3 à 5 jours après la vaccination, ces pourcentages étaient de 63%

(sur 8), 67% (sur 3), 35% (sur 20) et 22% (sur 9), respectivement, contre 75% (sur 8), 73% (sur 11), 33% (sur 21) et 50% (sur 36), respectivement, dans le cas des sujets ayant reçu l'IG 28 à 32 jours après vaccination. Il en a été conclu: 1) que les IG disponibles dans le commerce aux Etats-Unis d'Amérique contiennent couramment, outre des anticorps anti-poliovirus, des anticorps anti-virus amaril, et 2) que parmi les sujets qui, pour la plupart, sont immuns à l'égard de la poliomyélite, mais non à l'égard de la fièvre jaune, l'administration d'IG en même temps que la vaccination par le vaccin antipoliomyélitique buccal et le vaccin antiamaril, ou dans les 7 jours précédant la vaccination, ne diminue pas de manière significative les taux ou l'intensité des réponses en anticorps à ces vaccins. En ce qui concerne les volontaires initialement séronégatifs (titre 1:10) aux divers poliovirus, ils ont présenté des taux de réponse en anticorps et des titres maximaux qui n'ont pas semblé varier en fonction du moment de l'administration d'IG. Toutefois, le nombre de sujets étudiés ici était trop faible pour permettre de tirer des conclusions nettes.

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