(1%) for vomiting and diarrhoea to 471 (7%) for rhinitis and hay fever and 799 (11%) for wheeze. Between 20% and 30% of the children with each of these disorders has been perceived as being food intolerant. The potential for an increase in the proportion of children with these diseases being recorded as being food intolerant will depend largely on changes in the clinical appreciation of these issues and the parents' expectations from doctors. Though clinical judgment is the main criterion for diagnosis, and the diagnostic tests for a slow reaction to food are of low validity or cumbersome and time consuming, the number of children labelled as being food intolerant will increase in the community unless clear, simple, and credible criteria for diagnosis and management are worked out by specialists and general practitioners.

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Impaired responsiveness of homosexual men with HIV antibodies to plasma derived hepatitis B vaccine

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Abstract

Thirty five homosexual men (17 positive for antibody to the human immunodeficiency virus (HIV) and 18 consistently negative) were vaccinated against hepatitis B virus infection. Eight of the 17 seropositive patients failed to develop detectable hepatitis B surface antibody within three months of the third injection compared with only one of the 18 seronegative patients ($p<0.01$).

HIV infection is prevalent in the developed world in groups at risk for hepatitis B infection and in certain Third World countries where widespread vaccination programmes exist. This study shows the impact that coincident HIV infection may have on an otherwise efficacious vaccine. The efficacy of this and other vaccines in patients infected with HIV needs to be studied urgently.

Introduction

The immune dysfunction occurring during chronic infection with human immunodeficiency virus (HIV) does not consist only of a quantitative and qualitative abnormality of T helper or inducer lymphocytes. Other features include polyclonal B cell activation, with an increased number of B lymphocytes spontaneously secreting antibody, impaired in vitro B cell responsiveness to mitogens and antigens, and an impaired in vivo primary humoral response.[1]

There are areas in the Third World where HIV infection is already well established in the adult heterosexual population.[2,3] In these countries neonatal transmission is likely to become a dominant route of infection, leading to an increasing prevalence of infected and affected infants. Widespread vaccination programmes exist in many of these countries and are important for public health. In this context the possibility of a decrease in primary immune responsiveness in people infected with HIV is likely to have a profound effect on the efficacy of such programmes.

A vaccine against hepatitis B derived from plasma has been shown to be effective in controlled trials among homosexuals reported in 1980-3,[4-6] and trials conducted among other risk groups have confirmed its efficacy.[7-9] The vaccination of homosexual men has been shown to be cost effective in both the United States and the United Kingdom.[10,11] It has been recommended that susceptible homosexually active men should be vaccinated regardless of their ages or the duration of their homosexual practices.[12]

The largest trials of hepatitis B vaccines were carried out in the United States at a time when the prevalence of HIV infection was low. The prevalence of antibody to HIV among homosexuals in a cohort study in San Francisco, however, increased from 4·5% in 1978 to 67·3% in 1984[13] and from 3·7% in 1982 to 24·5% in 1986 among homosexual men in London attending this sexually transmitted disease clinic.[13a] The aim of this study was to examine whether the patient's responsiveness to hepatitis B vaccine was influenced by coexistent HIV infection.

Patients and methods

Thirty eight homosexual men were recruited between January and November 1985, 22 from a cohort study on the clinical course of HIV

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infection and 16 from men routinely attending this clinic. All consented to be tested for antibody to HIV, though some requested that they be kept ignorant of the result. Twelve men had asymptomatic persistent generalised lymphadenopathy (all positive for antibody to HIV), and the 26 others were asymptomatic. All were screened for syphilis, gonorrhoea, and non-specific genital infection and found to be clear. Serum samples taken immediately before the first injection of vaccine were all negative for hepatitis B surface antigen, hepatitis B surface antibody, and hepatitis B core antibody. None of the men had previously been vaccinated against hepatitis B.

All the men were injected with 20 μg H-B-Vax (Merck, Sharp and Dohme) immediately and after one month and six months. All injections were given in the same site—namely, the gluteal muscle—except in one patient who was positive for antibody to HIV, who received one injection in the arm. (The study began before it was reported that the response to hepatitis B vaccine was suboptimal if the vaccine was injected into the buttock.[14]) Immediately before each injection and three months after the last one 10 ml clotted blood was taken from the patient to test for hepatitis B surface antigen, hepatitis B core antibody, hepatitis B surface antibody, and HIV antibody, and serum was stored at −20°C. A general examination and full blood count were also performed on each patient.

Hepatitis B surface antigen was detected with a solid phase sandwich radioimmunoassay with a sensitivity of 0·5 ng/ml or less.[15] Hepatitis B core antibody was detected with a competitive radioimmunoassay and hepatitis B surface antibody with an immunometric radioimmunoassay as described previously.[16] The assay for hepatitis B surface antibody was used both qualitatively, as a screening test (sensitivity ≤0·01 World Health Organisation IU/ml), and quantitatively, to measure the response of hepatitis B surface antibody by comparing suitably diluted test serum samples with a calibration curve of WHO standards for hepatitis B surface antibody in the range 10-250 mIU/ml. Serum from each patient was measured in a single assay run, and the concentration of hepatitis B surface antibody present was quantified relative to that in the other patients and standardised against the WHO standard.

HIV antibody was detected with a competitive enzyme linked immunoassay (Wellcozyme anti-HTLV III, Wellcome Diagnostics). Data were analysed with Fisher's exact test and Mann-Whitney U test.

Results

Of the 38 men recruited, one was found to be suffering from hepatitis B (positive for hepatitis B surface antigen one month after the first dose). Of the remaining 37, two defaulted. The results presented therefore refer to the remaining 35 patients (18 consistently negative for antibodies to HIV and 17 positive). All 35 were negative for hepatitis B surface antigen and hepatitis B core antibody three months after the third injection (table). Only one of the 18 patients negative for HIV antibody did not have any detectable concentration of hepatitis B surface antibody three months after the third injection. This was in sharp contrast with eight of the 17 patients positive for HIV antibody who did not have hepatitis B surface antibody. This difference in response rate was significant ($p<0·01$, Fisher's exact test). Among the group positive for HIV antibody there was no significant difference in age between the responders and the non-responders. Among those who did respond to the vaccine there was no significant difference between the level of response in men who were positive for HIV antibody compared with that in men who were negative. The only seronegative patient who did not respond was mildly cytopenic on entry to the study (total white cell count $3·8\times10^9$/l), but he remained negative for HIV antibody. Among the patients positive for HIV antibody equal numbers of responders and non-responders to the vaccine (six of each) had persistent generalised lymphadenopathy. Only one of the seropositive men was leucopenic (total white cell count $3·5\times10^9$/l), and he failed to respond to the vaccine.

Discussion

This study shows that an adequate response to hepatitis B vaccination is significantly less likely to occur in homosexual men who are positive for HIV antibody than in those who are negative. This raises the problem of how to achieve a satisfactory response to the vaccine in those men who have failed to respond to the normal course and whether the currently recommended regimen needs to be altered in men who are known to be positive for HIV antibody.

The efficacy of vaccination is improved by injecting the vaccine in the arm rather than in the buttock, and non-responders should therefore be revaccinated in the arm.[12] Patients who have failed to mount an antibody response to the standard three dose course of vaccine may benefit from further injections of H-B-Vax. This boosted response of hepatitis B surface antibodies, however, is short lived among those who have a poor response to the first course of vaccine.[17]

Among those who responded to H-B-Vax in our study there was no significant difference in the level of response between the men who were positive for HIV and those who were negative, but the number who responded in the seropositive group was small. The long term immunogenic effect of H-B-Vax in patients who were positive for HIV should be assessed, as those who respond to the vaccine may show a more rapid decline in hepatitis B surface antibody concentration than seronegative subjects.

Hepatitis B surface antibody concentrations after H-B-Vax vaccination

Case No	Hepatitis B surface antibody concentration (mIU/ml)		
	1 month	6 months	9 months
	Seronegative patients		
1	30	350	700
2	750	500	2500*
3		20	400
4			600
5		100	800
6	NT		65
7			300
8			100†
9			200
10			50
11		150	5000
12			750
13			800
14			150
15			
16		70	1500
17		300	4500
18		10	30
	Seropositive patients		
19			
20		75	1500
21			
22		10	90
23			
24			
25			500
26		15	15
27			
28		100	6000
29		NT	600
30			
31		55	400
32			140
33			
34			
35			10

Where no value is given the concentration of hepatitis B surface antibody <10 mIU/ml. NT=not tested.
* Taken eight months after the third H-B-Vax injection.
† Taken four months after the third H-B-Vax injection.

Another possible way of improving the response rate is to give larger or more frequent doses of vaccine. In immunocompetent patients there seems to be little benefit in increasing the dose of vaccine.[18] The same does not apply, however, to the immunocompromised. A fourth dose of hepatitis B vaccine or three injections of a double dose improves the response of patients receiving dialysis.[9,19]

Our study also raises several questions relevant to medical practice in the United Kingdom and elsewhere. In the United Kingdom many homosexual men are already infected with HIV and are likely to respond poorly to conventional doses of the hepatitis B vaccine derived from plasma that is currently in use. In addition, dramatic changes in the sexual behaviour of homosexual men are reducing the risk of contracting sexually transmitted infections.[13a] In the light of these observations the cost effectiveness of the current vaccine policy should be re-examined. Furthermore, whether such impaired response rates will be seen with newer hepatitis B vaccines is unknown, but it would be wise during the trials of new vaccines to stratify the subjects according to the presence of HIV antibody and

explore the efficacy of larger doses or additional doses, or both, in those who are seropositive.

In global immunisation programmes the emerging pandemic of HIV infection must lead to a re-examination of the use of vaccines, particularly live ones, in neonates who are likely to be infected with HIV. This problem is most pressing in those countries in which a large proportion of women of childbearing age are seropositive. It affects both the vaccinee, because of failed vaccination or abnormal response to the vaccine, and the whole population, because of the increased burden of microbial infection through the failure of the public immunisation programmes.

In this study we show the impact that coincident HIV infection may have on an otherwise acceptably efficacious vaccine. The efficacy of this and other vaccines in patients infected with HIV needs to be studied urgently.

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SHORT REPORTS

From persistent generalised lymphadenopathy to AIDS: Who will progress?

About one third of people infected with the human immunodeficiency virus (HIV) have persistent generalised lymphadenopathy and are at risk of developing the acquired immune deficiency syndrome (AIDS). We report on the current rate of progression of persistent generalised lymphadenopathy to AIDS in a cohort of homosexual men in London and the value to the general physician of simple clinical markers for predicting the risk of progression.

Patients, methods, and results

One hundred and five patients who had persistent generalised lymphadenopathy were recruited from this clinic between November 1982 and April 1986 into a study of the clinical course of HIV infection. Five patients were lost to follow up. The remaining 100 patients were followed up for a median period of 24 months (range 9-50). Persistent generalised lymphadenopathy was defined as the presence of lymph nodes greater than 1 cm in diameter in two or more extrainguinal sites for at least three months, other causes for lymphadenopathy having been excluded. The patients were seen at intervals of three months, and all were consistently shown to be positive for HIV antibody by competitive enzyme linked immunosorbent assay (ELISA). From our previous clinical observations certain features stood out as possible predictors of AIDS—oral candida (found on examination and confirmed on culture) and, if present for more than three months, anaemia (haemoglobin concentration <13 g/l), leucopenia (<$4{\cdot}0\times10^9$/l), neutropenia (<$2{\cdot}0\times10^9$/l), lymphopenia (<$1{\cdot}5\times10^9$/l), thrombocytopenia (<150×10^9/l), and erythrocyte sedimentation rate >15 mm in the first hour. Data were analysed with Fisher's exact test and by calculating the relative risk.

Thirteen patients developed AIDS during a median follow up of 22 months (range 12-32). Five of these developed *Pneumocystis carinii* pneumonia, five Kaposi's sarcoma, one both, one *P carinii* pneumonia and cryptosporidiosis, and one cryptococcal meningitis. Oral candida were found in nine patients with persistent generalised lymphadenopathy. The following haematological abnormalities had been present for at least three months: anaemia (nine patients), leucopenia (19), neutropenia (18), lymphopenia (24), increased erythrocyte sedimentation rate (15), and thrombocytopenia (four). Oral candida and the first five of these haematological abnormalities were found to be associated with the later development of AIDS (table).

Comment

Of 100 patients with persistent generalised lymphadenopathy followed up for a median of 24 months, 13 developed AIDS. Using a life table technique we calculated that over three years the probability of patients with persistent generalised lymphadenopathy progressing to AIDS was 20·9%. Of the clinical features examined in our study oral candida, lymphopenia, an increased erythrocyte sedimentation rate, and anaemia were found to be the best predictors of the later development of AIDS.

Features associated with risk of progression to AIDS in 100 patients with persistent generalised lymphadenopathy

	Proportion of patients with abnormality who progressed to AIDS	Relative risk	Significance*	Median (range) time before onset of AIDS (months)
Oral candida	7/2	12	p<0·0005	8 (1-24)
Lymphopenia	9/15	7	p<0·0005	19 (2-33)
Erythrocyte sedimentation rate >15 mm in first hour	7/8	7	p<0·0005	23 (10-33)
Haemoglobin <13 g/l	5/4	6	p=0·002	18 (11-33)
Neutrophils <$2{\cdot}0\times10^9$/l	6/12	4	p=0·01	16·5 (2-21)
White cell count <$4{\cdot}0\times10^9$/l	6/13	4	p=0·02	16·5 (2-33)
Platelets <150×10^9/l	2/2	4	NS	18·5 (16-21)

*Fisher's exact test.