UK HAEMOPHILIA CENTRE DIRECTORS' HEPATITIS WORKING PARTY

GUIDELINES ON THE USE OF HEPATITIS B VACCINE

1. Background

Hepatitis B vaccine has been licenced in the UK for just over one year. A trial of hepatitis B vaccine at the Oxford Haemophilia Centre is nearly complete. Preliminary results of a trial of the Merck, Sharp and Dohme vaccine in Belgium and Sweden,[1] which compared the subcutaneous and intramuscular routes of injection in Haemophilia A patients and controls, showed that the immunogenicity was the same by either route.

Since the vaccine contains alum as an adjuvant, one would expect that the subcutaneous route would be associated with more side effects. A preliminary report on the experience at Oxford will be presented at the meeting on October 17th. The Belgian series so far contains only 8 patients, but they reported that the subjects given vaccine by the subcutaneous route tolerated the injections well.

2. Characteristics of the vaccine (H-B-vax Merck)

This consists of 20 micrograms (total protein) of inactivated hepatitis B surface antigen 22nm particles in a total volume of 1.0ml of diluent and contains alum as an adjuvant. It is given intramuscularly to normal individuals at time 0, 1, and 6 months as 3 doses. For patients with bleeding disorders, the same dose is given subcutaneously. The intradermal route should not be used as the product contains alum which may be associated with the appearance of skin nodules.

The vaccine should be stored at 4°C but not frozen; freezing has been shown to destroy the immunogenicity, probably by aggregating the suspended particles in the preparation. The vaccine is at present licenced for pre-exposure immunisation by the intramuscular route of persons over the age of six months. It is not licenced for use in pregnant women. The cost for a course of 3 injections is £63.50. This falls on the District Health Authorities, and therefore justification for the use of the vaccine in haemophiliacs has to be weighed against the needs of other groups of patients and staff in the NHS who would benefit. Haemophiliacs were included in the priority groups recommended by the DHSS.[2]

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3. The use of vaccine in haemophilia A patients

Groups who might be considered are:-

(a) Newly diagnosed haemophiliacs for whom treatment with blood products is anticipated
(b) Severe haemophiliacs (VIIIc <2%)
(c) Infrequently treated mildly affected patients requiring concentrate therapy to cover elective surgery.
(d) Patients with von Willebrand's Disease or Haemophilia B requiring factor VIII or IX concentrate in broad categories similar to those in (a), (b) and (c) above.

Household Contacts

(e) Household contacts of HBe antigen positive carriers of hepatitis B
(f) Sexual contacts of patients with acute hepatitis B.

4. Screening for seroimmunity

Anti-HBs antibody is highly correlated with immunity to hepatitis B. The only screening test that is sensitive enough is an immunoassay ie RIA or ELISA. The results must be expressed in International Units, usually milli-international units/ml. by comparison with a standard of known potency.

Anti-HBs tests cost at least £5.00 each, so the cost of screening must be balanced against the cost of immunisation. If the expected prevalence of anti-HBs antibody in any population is greater than 20%, then it is cost effective to screen for anti-HBs before immunisation. Since the prevalence rates of anti-HBs in severe haemophilia A patients is 70-80%, screening for anti-HBs should be done prior to immunisation.

Anti-HBc (hepatitis B core antibody) is the best index of past hepatitis B infection. It is also present in the serum of hepatitis B carriers and therefore does not correlate with immunity to hepatitis B. It can be used, however, to confirm doubtful positive tests for anti-HBs.

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5. Strategy for screening patients and relatives

Test	Result	Interpretation	Action
a) HBsAg	Positive		Do not immunise
b) Anti-HBs	Negative (<10 mille-iu/ml)	Not immune	Immunise
	Positive (>50 mille-iu/ml)	Immune	Vaccine not indicated
	Positive (between 10 and 50 mille-iu/ml)	Immune status doubtful	Test for anti-HBc
c) Anti-HBc	Positive (80% inhibition or more)	Immune	Vaccine not indicated
	Negative	Immunity still doubtful	Immunise

In some patients on regular factor VIII therapy, it is difficult to distinguish low levels of anti-HBs from passively acquired anti-HBs from recently administered factor VIII especially commercial factor VIII. If the patient's immune status is in doubt, the patient should be immunised and re-tested for anti-HBs one month later. Further follow up will depend on the results obtained. This specimen should be tested in parallel with the preimmunisation specimen.

6. Immunisation of staff of Haemophilia centres

It is doubtful whether staff at Haemophilia Centres are a high priority group for hepatitis B vaccine. There have been no reports to Oxford of transmission of hepatitis B from patients to members of staff. If screening for immune status is carried out then tests for HBsAg are best avoided. Advice about screening can be obtained from the nearest Public Health or Hepatitis Reference Laboratory.

7. Immune response to hepatitis B vaccine

This is slow compared with other vaccines. 70-80% of those immunised have protective levels of anti-HBs antibody 4 weeks after the second dose. The response after the third injection

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rises to over 90%. In individuals less than 30 years of age the response approaches 100%. The rate of none or poor responders is 6-7% in persons above the age of 50 years. Passive anti-HBs seems to have no effect on the immune response.

Due to the slow immune response, it would be theoretically desirable in certain patients to provide passive-active protection by the administration of hepatitis B immunoglobulin (HBIG) at the same time as the vaccine. This has been shown to be effective in non-haemophiliac patients.[3] Ideally a preparation of HBIG for intravenous use would be desirable. Unfortunately, the scarcity of HBIG means that it will not be available for use in this way in the foreseeable future. Moreover, hepatitis B vaccine is not licenced in the UK for passive/active immunisation.

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6.10.83

References

(1) Hepatitis B vaccination of Haemophiliacs, Desmyter J., Colaert J., Verstraete M., and Vermylen J. (1983) Scand. J. of Infect. Dis. Supplement 38, 42-45.

(2) Letter from the Chief Medical Officer, DHSS 82/13.

(3) Aspects of Vaccination against Hepatitis B, Deinhardt F. (1983) Scand. J. of Infect. Dis. Supplement 38, 17-23.

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