

DOES INTRADERMAL HEPATITIS B VACCINE WORK?

The hepatitis B vaccine used in NSW is of the recombinant or genetically engineered type. The genetic material within the DNA of the hepatitis B virus was initially cloned into the DNA of *Escherichia coli*, enabling the isolation of the S-gene and its incorporation into an expression plasmid containing the components necessary for replication and maintenance in yeast cells. Further manipulation enabled the transformed yeast cells to produce hepatitis B surface antigen (HBsAg)¹.

Hepatitis B vaccine is recommended for use in the following groups^{2,3}:

- 1 Households, institutions, schools
 - seronegative household contacts of a carrier
 - seronegative mentally retarded persons in care
 - seronegative children in kindergartens and primary school where there is a significant ethnic carrier population.
- 2 High-risk individuals
 - sexual partners and children aged less than five years of chronic carriers and acute hepatitis B patients
 - intravenous drug users
 - homosexuals with multiple partners
 - prostitutes
- 3 Health care workers, including health care profession students, mortuary attendants and some laboratory personnel
- 4 Babies born to carrier mothers and babies born into ethnic groups with high carrier rates
- 5 People receiving multiple transfusions/haemodialysis
- 6 Prisoners

Hospital personnel in contact with blood and body fluids are at significant risk of contracting hepatitis B. In the United States, Dienstag et al found a prevalence of markers of prior hepatitis B virus (HBV) infection in 16 per cent of health care workers⁴. In Australia the highest prevalence of HBV markers among health care workers was 16 per cent among the dental professions, and the highest prevalence among patients was 80 per cent in a group attending Sydney's Sexually Transmitted Diseases Clinic^{5,6}.

The vaccination schedule recommended for adults is a course of three injections of 1.0mL, with the second after a one-month interval and the third after a six-month interval following the initial injection. The prescribing information for the vaccine states it should be injected intramuscularly¹.

The reason for instituting the *intradermal* instead of the intramuscular route of vaccination was one of economy. It was believed the intradermal route was as efficacious as the intramuscular route. The vaccination program was not instituted for the purpose of a scientific survey and no specific consent was obtained. The cost difference between the course of vaccination and post-screening per health care worker was \$46.30 (73 per cent) less at 1988 prices, because a smaller intradermal dose was able to be used. Details are given in Table 5.

Some studies of health care workers or trainee health care workers found comparable seroconversion rates between the intramuscular and intradermal regimes^{8,9}.

TABLE 5

COST OF HEPATITIS B VACCINATION 1988*

Item	Intramuscular Route 1.0 mL Dose	Intradermal Route 0.1 mL Dose
Vaccine — 3 doses	\$54.00	\$ 7.70
Post-screening	\$ 9.20	\$ 9.20
Total cost per Health Care worker	\$63.20	\$16.90

*The hospital contract cost of hepatitis B vaccine per adult dose in March, 1991 is \$7.65.

Wilkins and Cossart found seroconversion to protective levels of antibodies to hepatitis B surface antigen (anti-HBs) in 89 per cent after four intradermal doses, but they used the first generation serum-derived vaccine which would have contained more antigenic material because of impurities, their cohort was young, and according to the methods description there was no follow-up after seroconversion⁹. Other studies found the intradermal route produced significantly lower levels of anti-HBs at all points measured up to 18 months; and 19 to 21 months^{10,11}.

Because of continuing problems with waning immunity at two hospitals following the intradermal course, the Central Western Health Region administration at Bathurst was asked this year to review the situation and to advise on remedial measures. We believe this is the first retrospective survey conducted in Australia of the intradermal administration of the second generation or recombinant hepatitis B vaccine where vaccinees were followed up for persistence of antibody levels. The vaccine used was Engerix-B, from Smith, Kline and French Laboratories Australia Limited, a product manufactured and imported from the parent company Smith Kline-RIT, Belgium.

METHODS

From April 1988, 161 health care workers at Parkes and Peak Hill hospitals, 400km west of Sydney, were given a course of 0.1mL (2 μ g) of vaccine by the intradermal route into the deltoid area. Timing of the schedule was the same as for intramuscular use (0, 1 and 6 months). Each single 1.0mL vial of vaccine for intramuscular use yielded seven doses of 0.1mL for intradermal use. The vaccine batches known to have been used were ENG165B4 until about November 1989, then ENG181A4, and later in 1990 ENG186B4, ENG639A4 and ENG628A4A. No screening for prior HBV infection was undertaken because of cost considerations.

Post-vaccination assays employed the Amersham ELISA test initially. Later in 1990 the Abbott Laboratories' Radioimmunoassay AUSAB was also used. Immunity was determined at ≥ 10 IU/L anti-HBs (or its equivalent by AUSAB).

The 161 subjects consisted of 36 males and 125 females. Among the 83 subjects whose age was recorded, the range was 24 to 63 with a mean age of 42 years.

TABLE 6

TYPICAL HEPATITIS B VACCINATION HISTORY OF A PARKES HOSPITAL HEALTH CARE WORKER WITHOUT A PROTECTIVE ANTIBODY LEVEL FOLLOWING THE INTRADERMAL COURSE

Date	Batch	Route	Test
31.5.88	ENG165 B4	ID	anti-HBs negative
28.6.88	ENG165 B4	ID	
14.12.89	ENG181 A4	ID	
21.2.89	ENG186 B4	IM	anti-HBs positive anti-HBs negative
22.3.89			
8.5.89			
16.7.90	ENG628 A4	IM	Test recommended — not yet undertaken
23.7.90			
21.8.90	ENG628 A4a	IM	
March 1991			

Initially those who did not demonstrate anti-HBs at ≥ 10 IU/L some two to three months after the intradermal course were offered a one-dose booster of 1.0mL of vaccine by the intramuscular route, and were retested about two months later. During the program it became apparent that the single boosters did not yield lasting protective antibody levels in many subjects. Some then received the full course of intramuscular injections following the intradermal course, without any intervening antibody assay, although such assays were available and were recommended in the event of sharps/needlesticks injuries.

RESULTS

i) Initial evaluation two-three months post-vaccination.

Of the 161 subjects, 103 (64 per cent) had anti-HBs at the protective level of ≥ 10 IU/L, and 58 (36 per cent) did not have anti-HBs to this level.

ii) Monitoring 18 months after the intradermal course.

Of the 103 who had anti-HBs after the course, 43 presented for retesting within 18 months. Of these 26 (60 per cent) had protective levels of anti-HBs, while in 17 (40 per cent) the immunity had waned to < 10 IU/L.

iii) Monitoring after the intradermal course and one intramuscular booster.

Of the 58 who failed to demonstrate anti-HBs ≥ 10 IU/L after the intradermal course, 29 (50 per cent) achieved protective levels after one intramuscular booster. Thirteen of these were tested again within 18 months. Only five (38 per cent) remained at protective levels and in eight (62 per cent) immunity had waned to < 10 IU/L. The antibody status of the other 16 is unknown. Detailed records were not available for the calculation of geometric mean titres.

iv) Typical profile

The recommendation was subsequently made that the intradermal course be followed by a three-dose intramuscular course. An example of a typical profile of procedures of one of the 58 health care workers, who did not have protective antibody levels after the intradermal course, is given in Table 6.

DISCUSSION

The present investigation was initiated when the Parkes and Peak Hill hospitals requested assistance with their hepatitis B immunisation program because immunity had waned in many vaccinees, following either the intradermal course or the subsequent intramuscular booster. The investigation was not designed to compare the intramuscular with the intradermal route, and some data that would have been required for such a comparison were therefore not collected.

In 1981 hepatitis B immunisation by the intramuscular route using serum-derived hepatitis B vaccine was shown to yield seroconversion in 96 per cent following a course of three injections (0,1, 6 months)⁷. The Parkes and Peak Hill hospitals' program of intradermal vaccination yielded protective levels of anti-HBs in only 64 per cent. We were disappointed with this response since it was lower than those reported in the initial trials by the intramuscular route. Of concern is that among the 64 per cent of subjects who had protective antibody levels after the course, they waned in 40 per cent within 18 months.

This is in contrast to antibody levels following the use of first generation vaccine by the intramuscular schedule, which are generally considered to remain at protective levels for more than five years, though two recent studies have shown they also wane within five years in 19 per cent and 35 per cent of adult subjects^{12,13}.

Furthermore, a single intramuscular booster following the intradermal course resulted in protective antibody levels in only half the subjects, and immunity again waned among 62 per cent within 18 months. It is probable that the immunological memory or anamnestic response would have been protective for some who subsequently contracted a HBV infection.

Based on these data, the use of the intradermal route with Engerix-B cannot be recommended. The only two recombinant hepatitis B vaccines licensed for use in Australia are Engerix-B and H-B-VAX II (Merck Sharp & Dohme). Both are recommended for intramuscular use^{1,14}.

As the yeast-derivation, immunogenicity and purified HBsAg content of H-B-VAX II is similar to Engerix-B, our results indicate that this vaccine would also need careful evaluation before intradermal use is adopted.

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From the data of the Red Cross Blood Transfusion Service and health care worker surveys, it is considered likely that between 5 and 10 per cent of the 161 subjects would have had prior markers of HBV infection if the pre-vaccination tests had been employed^{5,6}. Those from Peak Hill may have had a higher percentage of markers because of the high proportion of Aborigines in that town. For those who had previously acquired anti-HBs, the vaccine course would have boosted immunity, while it would have had no effect in the expected 0.5 per cent of HBsAg carriers, irrespective of the route of administration. Those with evidence of prior infection need not have been vaccinated.

There is no history of adverse factors, such as freezing the vaccine, a break in the cold chain or injection into adipose tissue, but the subject population had a mean age of 42 and it is known that in those over 40 years the seroconversion rate is lower following the intramuscular route of vaccine administration¹⁵. However, the intramuscular route response by age may not be equated to an intradermal response without the evidence of a clinical trial. Such an age bias is common among hospital employees in NSW country regions. Anti-HBs levels following intramuscular hepatitis B immunisation may not reach a peak until three months after the course¹⁶. The determination of assays in this program two to three months post-vaccination are considered not to have significantly affected the results obtained. The value of the post-vaccination assay for anti-HBs level is re-emphasised¹⁷.

In the Central Western Region those who had received the vaccine intradermally were recommended to have a course of three immunisations by the intramuscular route.

There is some evidence that health care workers elsewhere may be in a similar position because other institutions adopted hepatitis B vaccination by the intradermal route for their health care workers. It is recommended that an assessment of the situation be instituted by all Public Health Units in NSW and that other States be made aware of the finding.

The hospitals' responsibilities under the Occupational Health & Safety Act must be taken into consideration. These include the absolute obligation of the employer to ensure the employees are not subjected to a known health hazard. Given the disappointing results of the intradermal program the hospitals had a moral and legal obligation to pursue the workers' interests and initiate a remedial program, aimed at achieving successful immunity to hepatitis B. The initial economy considerations, which were the reasoning behind the intradermal program, would likely be outweighed by the compensation costs of a single successful court case, should a work-related infection take place where the

health care worker subsequently becomes a carrier of HBsAg. The economic consideration is also not relevant now as the vaccine price has been greatly reduced since 1988, and in March 1991 was \$7.65 per adult dose (hospital contract price).

Many procedures were required for each health care worker as can be seen from Table 5. Additional post-vaccination screening costs have been incurred by hospitals. There is now a degree of ill-feeling toward the intradermal program and some personnel may no longer be presenting for further vaccinations or antibody assays.

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