Intradermal hepatitis B vaccination in thalassaemia

S Leonardi, T Leggio, A Sciacca, F Di Gregorio, S Musumeci

Abstract

Fifty six children with thalassaemia, and 118 healthy subjects, who had all been immunised with an intramuscular injection of hepatitis B vaccine (HB-VAX) into the deltoid area three years previously, were given booster doses intradermally. All responders (good=hepatitis B surface (HBs) antibody titre ≥ 10 U/l; poor=HBs antibody titre < 10 U/l) showed pronounced increase in anti-HBs titre, in many cases above 1000 U/l. We also found positive HBs antibody response after further doses (two to four) at intervals of 15 days in non-responders (those patients who formerly had shown no HBs antibody titre after the conventional schedule of vaccination). The humoral response was always preceded by a delayed tissue hypersensitivity reaction. In conclusion, vaccine against hepatitis B virus given in low doses intradermally produces an effective immune response; it is a useful method of enhancing the antibody response in exposed patients, and of vaccinating those who do not respond initially.

Thalassaemic subjects who have been immunised against hepatitis B virus often need many booster doses to maintain their hepatitis B surface (HBs) antibody titre above 10 U/l. In addition, between 5 and 20% of subjects who have been vaccinated against hepatitis B virus do not respond to the hepatitis B surface antigen (HBsAg) after either conventional or booster vaccination.^{1 2} This, together with the number of thalassaemic patients presenting for vaccination, makes it potentially an extremely expensive procedure.

It has been shown that the immunising effect of hepatitis B vaccine given in low doses (2 μ g) intradermally is good in both patients who respond and in those who do not.³⁻⁵ Recently it was found that the antibody response after vaccination by the intradermal route as low doses (2 μ g) was comparable with that after vaccination by the standard intramuscular route (20 μ g).⁶

We report a study of intradermal revaccination in 56 thalassaemic patients who had been vaccinated about three years previously with hepatitis B vaccine (HB-VAX) given intramuscularly into the deltoid area.

Patients and methods

We studied 56 children with thalassaemia who had been immunised against hepatitis B virus three years previously with HB-VAX vaccine

given intramuscularly into the deltoid area. The children were grouped according to their anti-HBs titres into: non-responders—no detectable anti-HBs (n=11); poor responders—anti-HBs < 10 U/l (n=12); and good responders—anti-HBs ≥ 10 U/l (n=33). We also studied a control group of healthy medical staff, which included 15 non-responders, nine poor responders, and 94 good responders.

The vaccine was HB-VAX (Merck Sharp and Dohme) and it was given in doses of 5 μ g in 0.25 ml intradermally on the volar surface of the forearm. All patients were kept under observation for 48 hours after inoculation to assess the delayed hypersensitivity reaction. This was described as 'positive' if a cutaneous bleb appeared that was larger than 1 cm² in diameter. Two weeks after each revaccination dose had been given, serum was taken for assay of the anti-HBs titre; the inoculations were continued at two weekly intervals until the titre had risen above 10 U/l. HBs antibody titres were measured by radioimmunoassay (Ausab, Abbott Laboratories).

Results

All responders (45/56 children with thalassaemia and 103/118 healthy subjects) showed a delayed hypersensitivity reaction 48 hours after they had received the intradermal vaccine. In addition two of the 11 non-responders in the thalassaemic group, and three of the 15 in the healthy control group, showed a reaction 48 hours after the first dose. It took three doses, however, before all the non-responders had produced a reaction (table 1).

All poor responders (12 thalassaemic patients and nine healthy subjects) had developed HBs antibody titres of ≥ 10 U/l two weeks after the first intradermal dose. There was also a further increase in the HBs antibody titres of all the good responders in both groups (33 and 94, respectively). In all but two non-responding thalassaemic patients (two of 11, 82%) the anti-HBs titre was ≥ 10 U/l two weeks after the second intradermal dose, and even the remaining two had titres above 10 U/l after the fourth injection (table 1). In all the non-responding healthy subjects the anti-HBs titre had risen above 10 U/l after the second dose.

Many good responders in both groups showed increases in their antibody titres to ≥ 1000 U/l after a single dose of vaccine (table 2), and though only a few poor responders and non-responders showed titres of ≥ 1000 U/l after one dose, the titres increased with the number of doses that were given (table 2). After revacci-

Department of
Paediatrics,
University of
Catania, Italy
S Leonardi
T Leggio
A Sciacca
F Di Gregorio
S Musumeci

Correspondence to:
Dr Professor S Musumeci,
Department of Paediatrics,
University of Catania,
Viale Andrea Doria 6,
95100 Catania,
Italy.

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Table 1 Number of patients who achieved an antibody response (anti-HBs >10 U/l) at different times

	Good responders		Poor responders		Non-responders	
	Thalassaemic patients (n=33)	Healthy subjects (n=94)	Thalassaemic patients (n=12)	Healthy subjects (n=9)	Thalassaemic patients (n=11)	Healthy subjects (n=15)
48 Hours	33	94	0	0	0	0
Two weeks	33	94	12	9	5	6
Four weeks	0	0	0	0	9	15
Six weeks	0	0	0	0	10	15
Eight weeks	0	0	0	0	11	15

Table 2 Range of titres of HBs antibody after revaccination

HBs antibody titre (U/l)	Good responders (>10 U/l)		Poor responders (<10U/l)		Non-responders	
	Thalassaemic patients	Healthy subjects	Thalassaemic patients	Healthy subjects	Thalassaemic patients	Healthy subjects
<10	0	0	0	0	0	0
10-99	0	0	0	0	0	0
100-499	4	4	7	4	5	5
500-999	4	10	3	4	1	3
≥1000	25	80	2	1	5	7
Total No	33	94	12	9	11	15

Table 3 Maximum HBs antibody titres before and after intradermal reimmunisation. Figures are given as median (range)

	Good responders		Poor responders		Non-responders	
	Thalassaemic patients (n=33)	Healthy subjects (n=94)	Thalassaemic patients (n=12)	Healthy subjects (n=9)	Thalassaemic patients (n=11)	Healthy subjects (n=15)
Before reimmunisation	392 (256-512)	197 (100-333)	<10	<10	Not detected	Not detected
After reimmunisation	882 (333-1024)	950 (333-1024)	473 (256-1024)	577 (256-1024)	634 (256-1024)	675 (256-1024)

nation, all subjects in both groups—whether responder or not—showed similar median titres of anti-HBs (table 3).

Discussion

Our results show that low doses of vaccine against hepatitis B virus given intradermally can produce an effective immune response in thalassaemic patients, and we achieved complete success in revaccinating all responsive thalassaemic patients 36 months after their last dose of vaccine. They all showed both delayed hypersensitivity reactions and increased antibody titres.

Our findings also show that this method of vaccination can be successfully used in patients who initially did not respond. All subjects developed high titres of antibody as soon as we started revaccination.

All thalassaemic patients who have been vaccinated against hepatitis B virus require booster doses, and we believe that giving the doses intradermally is the most effective and economical way of doing it. Some authors have reported lower antibody titres after intradermal vaccination,^{9 10} but we saw increases of ≥1000 U/l in many of the good responders. Consequently over 90% of them will have antibody titres over 10 U/l after five years.^{11 12} In addition, all the poor responders achieved HBs antibody titres of over 100 U/l, and a few had titres of up to 1000 U/l, so that even though only a small percentage of them will lose their humoral immunity after four years,¹¹ they should be

given additional booster doses more often than the good responders.

The hypersensitivity skin reaction appears within 48 hours of each intradermal injection, is easy to monitor, and should motivate patients to accept the booster doses.

Miller *et al* found a low response rate to the intradermal injection in adults with congenital coagulation disorders (56%).¹³ Because their rate for children was 100%, they concluded that the decline was age related as a result of immune compromise by treatment for their original disease.

In conclusion, we believe that revaccination against hepatitis B virus by the intradermal route should be preferred in unresponsive cases.⁵ The use of low doses of vaccine given in this way can form the basis of a widespread and effective prophylactic regimen, especially in patients with thalassaemia who are being treated with multiple transfusions.

We are currently using the new genetically engineered vaccine against hepatitis B virus (Engerix B), and our experience so far confirms its efficacy when given intradermally in low doses.

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