Thrombocytopenic purpura as adverse reaction to recombinant hepatitis B vaccine

F Ronchi, P Cecchi, F Falcioni, A Marsciani, G Minak, G Muratori, P L Tazzari, S Beverini

Abstract

Three cases of immune thrombocytopenic purpura after the first dose of recombinant hepatitis B vaccine occurred in infants under 6 months of age. Other possible causes of this condition were excluded. Antiplatelet antibodies were present. A defect in platelet production was excluded in two children. Corticosteroid treatment was effective. Subsequent administration of other vaccines (against polio, diphtheria, and tetanus) did not cause relapse of thrombocytopenia.

(Arch Dis Child 1998;78:273-274)

Keywords: recombinant hepatitis B vaccine; thrombocytopenic purpura; antiplatelet antibodies

The recombinant hepatitis B vaccine, presently used worldwide, is highly immunogenic but is generally well tolerated. Serious adverse reactions such as anaphylaxis and polyradiculoneuritis,¹ demyelination of the central nervous system,² liver dysfunction and DNA antibodies,³ or Evan's syndrome (autoimmune haemolytic anaemia and thrombocytopenia⁴) are reported very rarely.

In 1994 Poullin and Gabriel⁵ reported the cases of two young females affected by thrombocytopenia after using recombinant hepatitis B vaccine, after the second and third dose respectively. In 1995, Meyboom *et al* reported 28 cases of thrombocytopenia after using hepatitis B vaccine,⁶ but different types of vaccines (recombinant and non-recombinant) were used in this study and only eight cases showed a possible relation between vaccine and thrombocytopenia.

Recombinant hepatitis B vaccine is routinely given to all children in Italy at 3, 5, and 12 months of age. Between March 1995 and May 1996 we observed thrombocytopenic purpura after the first dose of recombinant hepatitis B vaccine in three infants (under 6 months old).

Case report

CASE 1

This female infant was delivered normally at term weighing 3100 g and was breast fed. She was admitted for two days at 4 months of age for upper respiratory tract infection. On examination petechiae and splenomegaly were noted. The platelet count was $15 \times 10^9/l$. The remainder of the blood count was normal, as were assays of prothrombin and partial thromboplastin time, C3 and C4, and immune complexes. One month before, the first dose of recombinant hepatitis B vaccine (Engerix-B,

SmithKline Beecham) had been given to the baby, but no other vaccines were given. Until the time of hospital admission she had been in good health and had not received any drugs. Serological assays for adenovirus, mycoplasma, rickettsia, chlamydia, toxoplasma, rubella, cytomegalovirus, and herpes simplex, and cultures from blood, urine, and stools were negative, as were anti-HBs antibodies.

After 10 days in hospital she was discharged with a platelet count of $40 \times 10^9/l$ without treatment, and follow up was arranged. However, the parents sought a second opinion elsewhere and oral corticosteroid treatment (prednisone 2 mg/kg/d for two months) was given. The platelet count returned to normal and remained so over the following nine months. The infant subsequently received diphtheria, tetanus, and oral polio vaccines.

CASE 2

This male infant was delivered normally at term weighing 4100 g and was bottle fed. The infant remained well until the age of three months, when diphtheria, tetanus, oral polio, acellular pertussis, and recombinant hepatitis B (Engerix-B SKB) vaccines were given. Three weeks later he was admitted with purpura and splenomegaly. On admission the platelet count was $32 \times 10^9/l$. The remainder of the blood count was normal, as were assays of prothrombin and partial thromboplastin time, C3, and C4. Autoantibodies (antinative DNA and antinuclear antibodies) and immune complexes were absent, and serological assays and cultures (as in case 1) were negative. One week later, an assay for IgG and IgM antiplatelet antibodies—detected by direct and indirect testing with immunofluorescence staining and flow cytometry analysis, as already described⁷—was found to be positive. Cytology from bone marrow aspirate was normal. Oral corticosteroid treatment (prednisone 2 mg/kg daily) was started. After a week of treatment the platelet count increased to $469 \times 10^9/l$. This dose of prednisone was continued for a total of three weeks and then gradually reduced. After six months the platelet count remained normal. A second dose of diphtheria, tetanus, and oral polio vaccines was given to the infant three months after the end of the corticosteroid treatment. The platelet count remained normal over the following six months. No further doses of recombinant hepatitis B vaccine were given.

CASE 3

This male infant was delivered normally at term weighing 3300 g, and was breast fed. The infant remained well until the age of 3 months,

Divisione
Pediatria—Ospedale
Civile di Cattolica
(RN), Cattolica (RN),
Italy

F Ronchi
P Cecchi
F Falcioni
A Marsciani
G Minak
G Muratori
S Beverini

Servizio di
Immunematologia e
Trasfusionale—Policlinico
S Orsola, Bologna,
Italy
P L Tazzari

Correspondence to:
Dr F Ronchi, Divisione
Pediatria Ospedale di
Cattolica, Via Beethoven
41—47033 Cattolica (RN),
Italy.

Accepted 5 November 1997

when diphtheria, tetanus, acellular pertussis, oral polio, and recombinant hepatitis B (Engerix-B SKB) vaccine were given. After six days scanty petechiae appeared, and four days later he was admitted to hospital. The platelet count was $20 \times 10^9/l$ and all investigations were normal. These included the same assays and cultures as in cases 1 and 2 and also a bone marrow aspirate. An assay for antiplatelet antibodies (IgG and IgM) was positive. After 10 days the platelet count was $11 \times 10^9/l$ and oral corticosteroid treatment (prednisone 2 mg/kg daily) was started. After five weeks of treatment the platelet count had risen to $165 \times 10^9/l$. The treatment was gradually reduced and over the following six months the platelet count remained within normal limits.

Discussion

A causal relation between the use of a vaccine and this type of adverse reaction is hard to prove but is plausible if there is no known alternative cause, if the latency time is credible, and if there is evidence of a pathogenic mechanism which can be activated by the causal agent (vaccine) and which can cause the effect (thrombocytopenia).

The occurrence of thrombocytopenic purpura after administration of recombinant hepatitis B vaccine has been reported recently. The cases recognised by Poullin and Gabriel⁵ appeared after the second and the third dose of vaccine (with a latency time of three and four weeks respectively) in two subjects who, like our case 1, received only this vaccine. In our three cases, on the other hand, the thrombocytopenia appeared after the first dose of the vaccine and the latency times between vaccination and thrombocytopenia were four weeks, three weeks, and one week, respectively. The case with the shortest latency time showed the lowest platelet count and the longest duration of thrombocytopenia. None of our three patients had had previous bacterial or viral infections or were receiving any drugs, nor did we find clinical

or laboratory data suggestive of autoimmune disease. The platelet count rose to normal levels between three and eight weeks after initiation of steroid treatment in all cases.

While other vaccines in addition to hepatitis B vaccine were given to two of our three patients before the appearance of thrombocytopenia, the first patient received only recombinant hepatitis B vaccine. It remains possible that the thrombocytopenia in cases 2 and 3 was induced by one or more of the other vaccines given, but we are aware of no previous reports suggesting that possibility.

The pathogenesis of the thrombocytopenia in these cases appears to be immune mediated. In two cases we showed the presence of antiplatelet antibodies (IgG and IgM). In case 2 they were platelet bound and in case 3 they were both platelet bound and circulating. In neither case did bone marrow aspirate suggest a productive deficit of platelets. None of the three patients received any further doses of recombinant hepatitis B vaccine, though two received further immunisations against diphtheria, tetanus, and polio without relapse of thrombocytopenia.

The complete reversibility of thrombocytopenia in our three cases, and in cases described by others, confirms the benign nature of this extremely rare complication.

- 1 Stratton KR, Howe CJ, Johnston RB, eds. *Adverse events associated with childhood vaccines: evidence bearing on causality*. Washington, DC: National Academy Press, 1994.
- 2 Herroelen L, De Keyser J, Ebinger G. Central nervous system demyelination after immunisation with recombinant hepatitis B vaccine. *Lancet* 1991;338:1174-5.
- 3 Lilic D, Ghosh SK. Liver dysfunction and DNA antibodies after hepatitis B vaccination. *Lancet* 1994;344:1292.
- 4 Martinez E, Domingo P. Evan's syndrome triggered by recombinant hepatitis B vaccine. *Clin Infect Dis* 1992;15:1051.
- 5 Poullin P, Gabriel B. Thrombocytopenic purpura after recombinant hepatitis B vaccine. *Lancet* 1994;344:1293.
- 6 Meyboom RHB, Fucik H, Edwards IR. Thrombocytopenia reported in association with hepatitis B and A vaccines. *Lancet* 1995;345:1683.
- 7 Tazzari PL, Ricci F, Vianelli N, et al. Detection of platelet-associated antibodies by flow cytometry in hematological autoimmune disorders. *Ann Hematol* 1995;70:267-72.