Serum Sickness and Hepatitis B Vaccine Including Review of the Literature†

THASCHAWEE ARKACHAISRI, M.D.*

Abstract

HB vaccine is one of the most widely administered vaccines in the world. Its efficacy approaches 95 per cent. The majority of adverse reactions are generally mild, although there have been individual case reports of serious reactions since the vaccine has become commercially available. Here, a patient with a serum sickness-like reaction after her second HB immunization is reported. Review of the literature for reports of serious adverse reactions to the vaccine was also carried out.

Key word : Hepatitis B Vaccine, Serum Sickness, Adverse Reactions

ARKACHAISRI T
J Med Assoc Thai 2002; 85 (Suppl 2): S607-S612

The first hepatitis B (HB) vaccine was a plasma-derived vaccine. It was licensed in late 1981 and became commercially available in 1982(1). Despite an outstanding efficacy and safety record for these vaccines, reluctance to receive such products, driven by concerns of blood-borne infection transmission, interfered with successful, large-scale vaccination programs. This led to the development of an alternative vaccine that used genetic engineering techniques. Recombinant vaccines are produced from *Saccharomyces cerevisiae* (common baker's yeast) into which a plasmid containing the gene for

* Division of Pediatric Rheumatology, Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

† Part of this manuscript was presented at the 1997 American College of Allergy, Asthma and Immunology Annual Meeting in San Diego, CA.

hepatitis B surface antigen has been inserted. At present, there are two commercially available recombinant vaccines approved by the US FDA, i.e., Recombivax HB (Merk Sharp&Dohme), licensed in 1986, and Engerix B (SmithKline Beecham), licensed in 1989[1]. These vaccines contain more than 95 per cent HBs antigen protein, no more than 5 per cent yeast-derived protein, 0.5 mg/ml of aluminum hydroxide as an adsorbant and a 1:20,000 concentration of thimerosal as a preservative. Although no longer being used in this country, plasma-derived HB vaccines are produced inexpensively in other countries and have become the predominant form of vaccine used in much of Asia. In Thailand, there are several HBV available i.e. HBVAX II (Merk Sharp & Dohme), Hepatitis B Vaccine (Government Pharmaceutical Organization) Euvax-B (Aventis Pasteur), Hepavax-Gene (So Charoentrading), and Engerix B (GSK) and all are recombinant vaccines. In order to eliminate HB transmission, both the CDC and American Academy of Pediatrics have recommended administration of HB vaccine to all newborn infants[2]. Similar programs have been instituted in other countries successfully[3].

The efficacy of HB vaccination is 95-99 per cent in children and more than 90 per cent in adults after the third dose. The vaccine is less efficacious in premature infants and the elderly. Factors such as vaccine handling, immunization schedule, vaccine dose, site of injection, obesity, age and immunocompetancy may affect the efficacy as well [3]. The vaccine is generally safe. In large clinical trials, the majority of reactions were mild local reactions such as soreness at the injection site in 23 per cent and induration in 8 per cent. Generalized reactions such as fatigue may occurr in 15 per cent and headache in 9 per cent. No clinically important adverse effects directly related to vaccination have been recorded. In post-marketing surveillance of 4.5 million doses, only 307 adverse events have been filed. These include nausea, rash, headache, fever, malaise, injection site symptoms, vomiting, dizziness, arthralgia/myalgia, paresthesia and somnolence. The frequency of these symptoms range from 1:55,500 to 1:294,000 doses administered[4]. In about half of the reported cases, these adverse events occurred during the first 4 weeks following each of the 3 doses[5]. Although serious adverse reactions (life threatening or resulting in hospitalization or permanent disability) associated with HB vaccine administration were not encountered in the initial clinical trials, they have been reported in the literature as individual case reports. Here, the author reports a young girl who developed a serum-sickness like reaction after her second HB immunization. Case reports of serious adverse reactions between 1981-2001 were summarized.

CASE REPORT

A 13 year-old girl was in good health until about seven to ten days after her second HB vaccine (Engerix B, SmithKline Beecham Biologicals, Rixensart, Belgium) when she developed a generalized urticarial eruption. She took antihistamines with partial relief. Six to seven days later, she spiked a fever of 104°F and experienced malaise, diffuse arthralgias and arthritis involving both shoulders, elbows, knees and ankles. She developed morning stiffness lasting 10-15 minutes. She denied a history of preceding symptoms or other illnesses. She was not sexually active. There had been no reaction following the first HB vaccine.

On physical examination, she had an oral temperature of 100.8°F, a respiratory rate of 24/min, a pulse rate of 119/min and a blood pressure of 116/62 mmHg. She had a generalized urticarial rash involving her face, extremities, and trunk. She had one enlarged right anterior cervical lymph node (2 cm in diameter). She had symmetrical warmth, swelling and tenderness of wrists, knees and ankles with a limited range of motion of affected joints. The rest of the physical examination was unremarkable.

Laboratory evaluation performed at week four of the illness showed mild anemia and thrombocytosis (Hb 9.9 g/dl, Hct 30.3%, WBC 13,600/mm^3, PMN 55%, band 23%, lymphocytes 12%, monocytes 5%, eosinophils 3%, and platelets 615,000/mm^3). Her erythrocyte sedimentation rate was 126 mm/h. Hepatic and renal chemistry profiles were normal, a urinalysis was abnormal with 2+ proteinuria and microscopic hematuria. No casts were seen. Bacteriological culture of throat, blood and urine revealed no pathogens. At week five, her C3 was 255 (93-208 mg/dl), C4 was 35 (21-51 mg/dl), Raji cell was 13.5 ($\leq$15 mcg Eq/ml), C1q binding was 1.2 (<4 mcg Eq/ml), and an ASO titre was 147 (0-200 IU/ml). Hepatitis profile was negative for HBsAg, HBcAb, but positive for HBsAb.

Table 1. Summary of HB vaccination associated adverse reaction case reports.^ϕ

Age (y/o)	Sex	Type of vaccine	Sequence of vaccine	Lag period (days)	Reaction	HBsAg	HBsAb	Rechallenge
31	M	RHV*	1	2.5	Erythema multiforme	Neg	Pos	No
29	M	PDV#	2	10	Polyneuropathy	NA	Pos	NA
29	F	PDV	3	90	Erythema nodosum, hepatic Granuloma, Takayasu's arteritis	NA	Pos	No
59	M	NA	1	14	Polyneuropathy, cholestasis	Neg	Pos	No
24	F	RHV	2	15	Erythema nodosum	NA	NA	Yes
20	F	PDV	2	3	Acute posterior uveitis	Neg	Pos	Yes
19	M	PDV	1	14	Reactive arthritis	Neg	Pos	Yes
31	M	RHV	1	1	Polyarteritis, erythema nodosum	Neg	NA	No
43	F	RHV	1	4	Erythema nodosum	NA	NA	Yes
11	F	PDV	1	21	Transverse myelitis	Neg	Neg	NA
35	M	PDV	3	14	CNS demyelination	NA	Pos	NA
43	F	RHV	1	14	SLE	NA	NA	NA
33	M	RHV	2	2	Evan's syndrome	Neg	Neg	NA
36	F	RHV	3	30	Leukocytoclastic vasculitis	Neg	Pos	NA
50	M	RHV	2	30	Lichen planus	Neg	Pos	NA
45	F	RHV DLco	1	2	Raynaud's, arthralgia, decrease	NA	NA	NA
21	M	RHV	3	42	Glomerulonephritis	Neg	Pos	No
35	M	RHV	3	2	Cytolysis, hepatitis	Neg	Pos	NA
18	F	RHV	2	14	Leucoencephalitis	Neg	Pos	No
31	M	RHV	2	3	APMPPEE**	NA	NA	NA
43	F	RHV	1	10	Multiple sclerosis	Neg	NA	NA
26	F	RHV	2	10	Acute cerebella ataxia	NA	NA	No
15	F	RHV	3	28	Autoimmune thrombocytopenia	NA	Pos	NA
21	F	RHV	2	21	Autoimmune thrombocytopenia	NA	Pos	NA
4 mo	F	RHV	1	30	Autoimmune thrombocytopenia	NA	Neg	No
3 mo	M	RHV	1	21	Autoimmune thrombocytopenia	NA	Neg	No
3 mo	M	RHV	1	6	Autoimmune thrombocytopenia	NA	Neg	No
40	F	RHV	2	14	Nephrotic syndrome	Neg	NA	NA
18	F	RHV	2	10	Necrotic, bullous purpura	Neg	NA	NA
23	F	PDV	3	1	MEWDS***	NA	NA	No
27	M	RHV	1	8	Acute retinal vein occlusion	Neg	Neg	Yes
26	F	RHV	1	7	SLE	NA	NA	NA

* RHV = Recombinant Hepatitis B Vaccine, # PDV = Plasma-derived Vaccine
** APMPPEE = Acute posterior multifocal placoid pigment epitheliopathy & eosinophilia
*** MEWDS = Multiple evanescent white dot syndrome
^ not include anaphylaxis and other neurologic reactions (see text).
ϕ reference 11-37.

Beginning at week four of her illness, she was treated with Ibuprofen at 600 mg t.i.d. and cetirizine 10 mg qd. After two weeks of this regimen, there was no significant change in her skin and joint symptoms. She was then started on oral prednisone 40 mg a day. All her symptoms resolved quickly. The steroids were slowly tapered and discontinued by the eighth week. She has remained symptom free for the following 12+ months. She has not received a third HB vaccine.

DISCUSSION

Serum-sickness is a self-limiting immune-complex mediated disease, which occurs under conditions of antigen and antibody equivalency. It occurs following any heterologous antiserum administration. With a declining use of such sera today, the most common cause of serum-sickness reaction is secondary to drug administration, especially the β-lactam antibiotics(6). Serum-sickness typically occurs six to 21 days after administration of the inciting

antigen, and results in a broad range of symptoms: fever/malaise in almost all patients, cutaneous manifestations in about 95 per cent, mostly urticaria, arthritis or arthralgia, which is typically symmetrical, polyarticular and affecting large joints in 10-77 per cent of affected individuals; modest renal involvement, including proteinuria, microscopic hematuria, and rarely, clinically significant glomerular disease; rarely seen are lymphadenopathy/hepatosplenomegaly, mild gastrointestinal symptoms, myocardial and pericardial inflammation, systemic vasculitis, and peripheral neuritis[6-8]. The diagnosis of serum-sickness is based primarily on clinical history and physical examination as laboratory evaluations are usually not helpful[7,8].

The studied patient developed an urticarial rash one week after receiving HB vaccine. She then developed high fever, symmetrical polyarticular arthritis, proteinuria, microscopic hematuria, thrombocytosis, and an elevated ESR. The temporal relationship of her illness to the second HB vaccination suggests the diagnosis of serum-sickness, although a concurrent viral infection can not be completely ruled out. Post-streptococcal reactive arthritis and acute rheumatic fever are unlikely as she had no preceding illness, no evidence of previous streptococcal infection and a normal ASO titer. Even less likely would be the Gianotti-Crosti syndrome seen with natural hepatitis B infection, which is a benign, self-limiting disease occurring in young children, and characterized by the appearance of monomorphous, nonpruritic, dusky or coppery red, flat-topped, firm papules forming a symmetrical eruption on the face, buttocks and limbs, including the palms and soles, along with malaise and other mild constitutional symptoms. The absence of HBc antibody production argues against this possibility.

Musculoskeletal complaints have been previously described after HB immunization in two large uncontrolled population-based studies. In a study from New Zealand involving 166,757 children given a plasma-derived vaccine[2], arthritis or arthralgia occurred on only 12 occasions in 10 individuals. This accounted for less than 1 episode in 10,000 vaccinees[2]. In another study of 43,618 Alaskan HB vaccinees receiving 101,360 doses of plasma-derived HB vaccine, only 12 individuals developed arthralgia or arthritis lasting more than three days. This accounts for less than 1 episode in 3,000 vaccinees. One individual developed an Arthus reaction with a positive skin test with plasma-derived HB vaccine[2,9]. The Vaccine Adverse Event Reporting System (VAERS) identified 57 individuals who developed arthritis within two months after such vaccination between November 1990 and July 1992 [2]. Of these, 17 individuals had polyarthritis occurring within three weeks of vaccination, which was associated with fever. Nine of the 17 had transient rashes, accompanied by arthritis and fever. Only 3 patients had a symmetrical polyarthritis typical of serum-sickness. Interestingly, two individuals developed more chronic arthritis that persisted for more than 1 year[2]. Other vaccines which have been associated with serum-sickness like reactions include the rabies vaccine and tetanus toxoid[10].

Cumulative case reports of serious adverse reactions following the HB immunization since 1981, are summarized in Table 1. There have been 4 cases of anaphylaxis and several other cases of neurological reactions including Guillain-Barre syndrome (GBS), Bell's palsy, lumbar radiculopathy, brachial plexus neuropathy and optic neuritis[38]. Wise et al reported 60 cases of hair loss following routine immunizations[39]. Forty-six cases were associated with HB immunization, and in 3 of these cases (2 infants and one woman), symptoms recurred with reimmunization[40]. More recently, Niu et al evaluated the neonatal (0-28 days) death reported to VAERS, and found only 18 deaths out of 1771 neonatal reports. The cause of death for the 17 cases that underwent autopsy were sudden infant death syndrome in 12, infection in 3 and 1 case each of intracerebral hemorrhage, accidental suffocation, and congenital heart disease[41].

Although the cause-and-effect relationship of those serious adverse reactions to HB vaccine administration is controversial, the case presented here supports an association. Physicians should be aware that vaccination can lead to significant health problems, although the risk is small. Calculation of the relative risk of these reactions is not simple, since it depends on the diagnostic classification of the cases, estimation of the number of vaccinees, and knowledge of the background incidence of similar symptom complexes. No conclusive epidemiological associations have been made between HB vaccinations and these reactions. The benefits of the vaccine certainly outweigh the risk of any of these adverse events.

(Received for publication on February 1, 2002)

REFERENCES

1. Zannolli R, Morgese G. Hepatitis B vaccine: Current issues. Ann Pharmacother 1997; 31: 1059-67.
2. Stratton KR, Howe CJ, Johnston RB, et al. Hepatitis B vaccines. Ch 8. In: Adverse events associated with childhood vaccines: evidence bearing on causality. Stratton KR, Howe CJ, Johnston RB. (Eds), Washington D.C.: National Academy Press, 1994: 211-35.
3. Katkov WN, Dienstag JL. Hepatitis vaccines. Gastroenterol Clin North Am 1995; 24: 147-59.
4. Carmeli Y, De-Medina T. Serious hepatitis B vaccine adverse reactions, are they immune-mediated? Letter to the Editor. Vaccine 1993; 11: 1358-9.
5. De Serres G, Duval B, Boulianne N, et al. Importance of attributable risk in monitoring adverse events after immunization: Hepatitis B vaccination in children. Am J Pub Hlth 2001; 91: 313-5.
6. Lawley TJ, Frank MM. Immune complexes and allergic disease. Ch 38. In: Allergy : Principle and Practice. Middleton, jr E, Reed CE, Ellis EF, et al (Eds), St. Louis: Mosby, 1993: 4th Ed, 990-1004.
7. Erffmeyer JE. Serum sichness. Ann Allergy 1986; 56: 105-205.
8. Deswarte RD. Drug allergy. Ch 16. In: Allergic diseases: Diagnosis and Management. Patterson R, Grammer LC, Greenberger PA, et al. (Eds), Philadelphia: JB Lippincott Company, 1993: 4th Ed, 395-552.
9. McMahon BJ, Heiminiak C, Wainwright RB, et al. Frequency of adverse reactions to hepatitis B vaccine in 43,618 persons. Am J Med 1992; 92: 254-6.
10. Warrington RJ, Martens CJ, Rubin M, et al. Immunologic studies in subjects with a serum sickness-like illness after immunization with human diploid cell rabies vaccine. J Allerg Clin Immunol 1987; 79: 605-10.
11. Feldshon SD, Sampliner RE. Reaction to hepatitis B virus vaccine. Ann Intern Med 1984; 100: 156-7.
12. Ribera EF, Dutka AJ. Polyneuropathy associated with administration of hepatitis B vaccine. N Engl J Med 1983; 309: 614-5.
13. Castresana-Isla CJ, Herrera-Martinez G, Vega-Molina J. Erythema nodosum and Takayasu's arteritis after immunization with plasma derived hepatitis B vaccine. J Rheumatol 1993; 20: 1417-8.
14. Snider GB, Gogate SA. A possible systemic reaction to hepatitis B vaccine. JAMA 1985; 253: 1260-1.
15. Di Giusto CA, Bernhard JD. Erythema nodosum provoked by hepatitis B vaccine. Lancet 1986; 2: 1042.
16. Fried M, Conen D, Conzelmann M, et al. Uveitis after hepatitis B vaccination. Lancet 1987; 2: 631-2.
17. Hachulla E, Houvenagel E, Mingui A, et al. Reactive arthritis after hepatitis B vaccination. J Rheumatol 1990; 17: 1250-1.
18. Rogerson SJ, Nye FJ. Hepatitis B vaccine associated with erythema nodosum and polyarthritis. BMJ 1990; 301: 45.
19. Goolsby PL. Erythema nodosum after Recombivax HB hepatitis B vaccine. N Engl J Med 1989; 321: 1198-9.
20. Trevisani F, Gattinara GC, Caraceri P, et al. Transverse myelitis following hepatitis B vaccination. J Hepatol 1993; 19: 317-8.
21. Kaplanski G, Retornaz F, Durand JM, et al. Central nervous system demyelination after vaccination against hepatitis B and HLA haplotype. J Neurol Neurosurg Psychiatr 1995; 58: 758-9.
22. Tudela P, Marti S, Bonal J. Systemic lupus erythematosus and vaccination against hepatitis B. Nephon 1992; 62: 236.
23. Martinez E, Domigo P. Evan's syndrome triggered by recombinant hepatitis B vaccine. Clin Infect Dis 1992; 15: 1051.
24. Mathieu E, Fain O, Krivitzky A. Cryoglobulinemia after hepatitis B vaccination. N Engl J Med 1996; 335: 355.
25. Aubin F, Angonin R, Humbert P, et al. Lichen planus following hepatitis B vaccination. Arch Dermatol 1994; 130: 1329-30.
26. Allen MB, Cockwell P, Page RL. Pulmonary and cutaneous vasculitis following hepatitis B vaccination. Thorax 1993; 48: 580-1.
27. Carmeli Y, Oren R. Hepatitis B vaccine side effect. Lancet 1993; 341: 250-1.
28. Germanaud J, Causse X, Trinh DH, et al. A case of severe cytolysis after hepatitis B vaccination. Am J Med 1995; 98: 595.
29. Manna R, De Santis A, Oliviero, et al. Leucoencephalitis after recombinant hepatitis B vaccine. J Hepatol 1996; 24: 764-5.
30. Brezin AP, Lautier-Frau M, Hamedani M, et al. Visual loss and eosinophilia after recombinant hepatitis B vaccine. Lancet 1993; 342: 563-4.
31. Penneys NS. Multiple sclerosis and hepatitis B vaccination. Clin Infect Dis 1993; 17: 928.
32. Deisenhammer F, Pohl P, Bosch S, et al. Acute cerebellar ataxia after immunization with recombinant hepatitis B vaccine. Acta Neurol Scand 1994; 89: 462-3.
33. Macario F, Freitas L, Correia J, et al. Nephrotic syndrome after recombinant hepatitis B vaccine. Clin Nephrol 1995; 43: 349.
34. Baglivo E, Safran AB, Borruat FX. Multiple evanescent white dot syndrome after hepatitis B vaccine. Am J Ophalmol 1996; 122: 431-2.

35. Devin F, Roque G, Disdier P, et al. Occlusion of central retinal vein after hepatitis B vaccination. Lancet 1996; 347: 1626.
36. Guiserix J. Systemic lupus erythematosus following hepatitis B vaccine. Nephron 1996; 74: 441.
37. Ronchi F, Cecchi P, Falcioni F, et al. Thrombocytopenic purpura as adverse reaction to recombinent hepatitis B vaccine. Arch Dis Child 1998; 78: 273-4.
38. Shaw FE, Graham DJ, Guess HA, et al. Postmarketing surveillance for neurologic adverse events reported after hepatitis B vaccination. Am J Epidemiol 1988; 127: 337-52.
39. Wise RP, Kiminyo KP, Salive ME. Hair loss after routine immunizations. JAMA 1997; 278: 1176-8.
40. ACIP. Recommendation of the Advisory Committee on Immunization Practices (ACIP) : Update: vaccine side effects, adverse reactions, contraindications, and precautions. MMWR 1996; 45 (RR-12).
41. Niu MT, Salive ME, Ellenberg SS. Neonatal death after hepatitis B vaccine: The vaccine adverse event reporting system, 1991-1998. Arch Pediatr Adolesc Med 1999; 153: 1279-82.

วัคซีนไวรัสตับอักเสบบี กับ serum sickness และทบทวนบทตีพิมพ์ ผลข้างเคียงที่รุนแรงหลังจากการให้วัคซีน†

*ธัชวีร์ อรรคฉายศรี, พ.บ.**

วัคซีนตับอักเสบบี ถือเป็นวัคซีนชนิดหนึ่งที่ถูกใช้แพร่หลายทั่วโลก ผลการตอบสนองค่อนข้างสูงถึง 95% ของการฉีด ผลข้างเคียงโดยส่วนใหญ่เป็นแบบไม่รุนแรง แต่มีการรายงานผลข้างเคียงแบบรุนแรงจากการให้วัคซีนตัวนี้ บทความต่อไปนี้จะเป็นการรายงานผู้ป่วยเด็กซึ่งได้รับวัคซีนตับอักเสบบี เกิดอาการ serum sickness รวมทั้งทบทวนบทความหรือบทรายงานผลข้างเคียงแบบรุนแรงที่เคยตีพิมพ์หลังจากวัคซีนถูกนำมาใช้ทางคลินิก

คำสำคัญ : ไวรัสตับอักเสบบี, serum sickness, ผลข้างเคียง

ธัชวีร์ อรรคฉายศรี
จดหมายเหตุทางแพทย์ ฯ 2545; 85 (ฉบับพิเศษ 2): S607-S612

* หน่วยโรคข้อและรูห์มาติกเด็ก, ภาควิชากุมารเวชศาสตร์, คณะแพทยศาสตร์ศิริราชพยาบาล, มหาวิทยาลัยมหิดล, กรุงเทพ ฯ 10700

† ส่วนหนึ่งของบทความนี้ได้เสนอเป็นผลงานทางวิชาการในการประชุมประจำปีของ American College of Allergy, Asthma and Immunology ปี 1997 ณ San Diago, CA.