Hepatitis B vaccine—A hospital experience

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The recent introduction of long-term active immunity to hepatitis B by the Heptavax-B® vaccine is a major breakthrough in protection of high risk individuals to hepatitis B. However, the authors' timely experience and increased data lend question to the effectiveness of the presently used protocol, suggesting that a more predictable protocol along with post-screening be used to assure effective immunity to hepatitis B.

The situation
A 28-year-old white female is brought to the operating room for cholecystectomy. The routine preoperative laboratory results and her history do not reveal anything significant. When starting the patient's IV, the anesthetist inadvertently gets pricked with the needle from the used introducer. The puncture wound bleeds slightly and is cleansed with alcohol. Although an incident report is filed following hospital protocol, due to the “supposed” low risk of this patient, coupled with the anesthetist's completion of the Heptavax B® (hepatitis B vaccine, MSD) immunization program, no further followup is deemed necessary. Seven weeks later the anesthetist complains of fatigue and flu-like symptoms. The symptoms persist along with darkening of the urine and jaundice of the sclera. A complete liver profile is done to rule out all probable causes. A diagnosis of hepatitis B is made.

The anesthetist is treated symptomatically and, following a 10-month convalescence, is able to return to full clinical practice.

This scenario, which could have occurred anywhere in the country today, demonstrates the potential risk of hepatitis B to health care workers who may have direct blood contact. However, the anesthetist in this case was supposedly protected from contracting hepatitis B due to immunization with Heptavax-B® vaccine.

The disease
Hepatitis, inflammation of the liver, may be secondary to disorders as amebic dysentery, cirrhosis or infectious mononucleosis; may be drug or alcohol induced; may be caused by chemicals; or may be due to a viral infection. The viruses capable of causing liver inflammation that are of concern to health care workers include hepatitis A; hepatitis B; and non-A, non-B hepatitis. A review of the incubation, transmission, and serological markers will help to show the differences among these three diseases (Table 1). Of the three types, hepatitis B is the one of greatest concern to health care workers.

Because of the lengthy incubation period (six weeks to six months) and the transmission modes of hepatitis B, tracing of contacts and determination of inoculation is extremely difficult. One investigation revealed 16 cases of clinical hepatitis in medical personnel in four hospitals during a three-year period. Another comprehensive study over a four and a half year period identified 79
cases of hepatitis in employees of a university hospital. Of these, 68 were either dialysis unit or laboratory personnel. The majority of cases were shown to be of hepatitis B and were closely correlated to increasing exposure to blood from the dialysis transplant unit.\(^2\)

A more startling study traced an outbreak of hepatitis B involving four medical personnel members and the subsequent transmission of the disease to two hospitalized patients. In this study, four cases of hepatitis B occurred in hospital staff during a two-month period. Three months later, two patients who had been hospitalized when the staff had been infected, also developed acute hepatitis B. Transmission to these patients may have occurred via the arterial cannulae from a severe exudative dermatitis on the hand's of a therapist with the disease.\(^3\)

Chronic hepatitis B carrier state occurs in 6-10% of individuals following acute hepatitis B. However, carriers of HBsAg frequently give no history of recognized acute hepatitis. (Table II.) The Centers for Disease Control (CDC) estimates that there are approximately 400,000 to 800,000 infectious carriers of hepatitis B virus in the United States and this pool of carriers grows by 2-3% (8,000 to 16,000) annually. Chronic carriers represent the largest human reservoir of hepatitis B virus. Hepatitis B carriage is also associated with 4,000 deaths from cirrhosis and 800 deaths from liver cancer each year.\(^4\)

A search has been ongoing for an effective immunization against hepatitis B due to its increasing prevalence and high mortality and mor-

### Table I
**Characteristics of the hepatitis viruses**

<table>
<thead>
<tr>
<th></th>
<th>Hepatitis A</th>
<th>Hepatitis B</th>
<th>Non-A, Non-B Hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incubation period</td>
<td>3-6 weeks</td>
<td>6 weeks-6 months (average 2-3 months)</td>
<td>2-26 weeks (average 8 weeks)</td>
</tr>
<tr>
<td>Transmission</td>
<td>Fecal-oral; person to person; contaminated food, water, shellfish</td>
<td>Parenteral: blood to blood via needlestick or transfusion. Inapparent parenteral: infectious serum contact with abraded skin or cuts, on mucous membranes, splash into eyes; sexual contacts</td>
<td>Parenteral: primarily by transfusions, also by needlestick. Inapparent parenteral: (same as hepatitis B)</td>
</tr>
<tr>
<td>Serological markers</td>
<td>IgM anti-A, IgG anti-A</td>
<td>HBsAg, Anti-HBs, HBeAg, Anti-HBe, and Anti-HBc (HbcAg found only in liver—does not circulate)</td>
<td>Unknown—disease of exclusion</td>
</tr>
</tbody>
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### Table II
**Patients who may be under suspicion as hepatitis B carriers**

1. All patients with liver disease however acute or chronic.
2. Patients undergoing hemodialysis, or who have had a renal transplant.
3. All patients with leukemia, reticuloses, polyarteritis nodosa or polymyositis.
4. Patients being treated with radiotherapy or immunosuppressive drugs.
5. Immigrants or visitors from countries with a high background of carriers.
6. Persons who have been transfused in or recently returned from countries with a high background incidence (namely tropical and sub-tropical areas and Greenland).
7. Patients who have received blood or a blood product in the last six months, or who have been transfused with blood or blood products from paid blood donors.
8. Inmates of prisons or institutions for the mentally defective.
9. Drug addicts, prostitutes, and homosexuals.
10. The tattooed.
11. Those who have had their ears pierced recently.
12. Household contacts of HBV carriers.
13. Staff of institutions for the mentally retarded.

Sources:
bidity. Historically only passive post-exposure immunization had been employed, which consisted of gamma globulin and more recently HBIG (hepatitis B immune globulin).

Gamma globulin (immune serum globulin) is a sterile solution of antibodies (immune globulins) from human plasma. It is prepared by cold ethanol fractionation of large plasma pools and contains 10-18% protein. Immune serum globulin, produced in the United States after 1977, contains antibodies against hepatitis A and B viruses. Its primary effect is the introduction of these antibodies into the system, thus providing passive immunity which lasts approximately six months. Individuals exposed to hepatitis A or B must receive gamma globulin within seven days of exposure. It has been shown that gamma globulin provides minimal effectiveness in the prevention of clinical hepatitis.

HBIG is also a sterile solution of immune globulins prepared by cold ethanol fractionation. It is pooled from the venous plasma of individuals with high titers of antibodies to the hepatitis B surface antigen (anti HBs). Studies have shown that HBIG is effective in preventing clinical hepatitis in 75% of exposed individuals treated with this immune globulin. It is most effective if given immediately, no greater than seven days post exposure, and repeated in 30 days. HBIG when given in its two dose protocol has been shown to be superior to immune serum globulin in passive, post-exposure immunization.

However, both gamma globulin and HBIG produced short-term, passive post-exposure immunity. Consequently, there was still a void for the high-risk health care worker who was unaware of having been exposed to hepatitis B.

Development of Heptavax-B® vaccine

The groundwork for active immunization against hepatitis B was laid by Krugman and his associates during research done from 1970 to 1973. In a series of studies, the hepatitis B surface antigen was found to be immunogenic and protective against hepatitis B infection. This led to the development of hepatitis B vaccine (Heptavax-B®). This vaccine consists of a highly purified form of inactivated HBsAg particles derived from plasma of chronic carriers of the antigen.

This sub-unit of the hepatitis B virus, the noninfectious hepatitis B surface antigen, circulates in the plasma of the hepatitis B carriers and is harvested for the production of the hepatitis B vaccine.

The vaccine has a long complex production cycle, requiring approximately 65 weeks. Each lot undergoes a seven-step purification process designed to inactivate infectious hepatitis B virus, as well as representatives of all known groups of animal viruses, including immune deficiency syndrome (AIDS). The question of AIDS being a potential complication has been raised, given that since 1979, homosexual men (including those from cities with reported AIDS cases) have been primary donors for much of the plasma.

The vaccine development process relies on both the biophysical elimination of infectious particles and the subsequentially applied chemical inactivation steps. As a final test, doses of each vaccine lot are inoculated intravenously into chimpanzees.

Once the vaccine was produced, controlled clinical trials were conducted on 19,000 individuals over an eight year period. The vaccine was licensed for marketing by the U.S. Food and Drug Administration in November, 1981. Since its release, the vaccine has been given to more than 200,000 individuals with no reported transmission of hepatitis B; non-A, non-B hepatitis; or acquired immune deficiency syndrome (AIDS).

One hospital's experience

Since the vaccine's availability, many hospitals have developed policies for its use in high-risk em-
ployees. Because of the results of the previously mentioned studies, The Washington Hospital in Washington, Pennsylvania began a voluntary Hepatitis B (Heptavax-B®) Screening and Immunization Program in December, 1982.

The Washington Hospital's Infection Control Committee determined the areas and personnel groups considered at high risk to hepatitis B exposure. This was based on numerous studies which demonstrated a correlation of certain high-risk health care groups by job classification and frequency of blood contact (Table III). Based on these studies, the following groups were designated as high risk:

1. Laboratory personnel (working with blood products).
2. Pathologists.
3. Registered nurses and physicians in the emergency department.
4. IV teams.
5. CRNAs.
6. Operating room nurses and technicians.
7. Nurses working in oncology and in the gastrointestinal laboratory.

A formal education program was presented to these groups of individuals. The program encompassed: showing of a film “Hepatitis B Health Care Personnel at Risk” (provided by the vaccine manufacturer*); explaining the epidemiology of hepatitis B as it relates to the hospital setting (information provided by the infection control group); explaining the development of Heptavax-B® including immunization protocol and efficacy of the drug (information provided by the employee health group); and distributing available pertinent literature.

The high risk individuals were informed that the program was strictly voluntary, and a consent for screening and potential immunization was required. The individuals who agreed to participate in this program had a blood sample drawn (Anti-HBc) to determine their antibody status. This serological marker was chosen for use since it lasts longer than the Anti-HBs and denotes previous exposure to HBsAg and therefore immunity to the hepatitis B virus. Of those individuals agreeing to participate in the program, the following results were obtained: 8% were found to be serologically positive, requiring no immunization and the remaining 92% were found to be serologically negative, requiring the need for the immunization which was subsequently done.

Based on the reported high efficacy of the vaccine, (manufacturer's clinical trials indicated a 95-98% seroconversion following the three dose protocol), post-screening was not felt to be cost-effective. A laboratory technician, who was three months post-completion of the Heptavax-B® three dose protocol, requested serological screening to determine her antibody status. She was found to be seronegative. Consequently, the manufacturer was contacted to reconfirm the statement that measurable antibody responses should be within four to six weeks following the completion of the Heptavax-B® protocol.

The manufacturer's response was the recommendation that a fourth dose of the vaccine be given to effect a boost in the antibody response, allowing a six week waiting period and then a retest. After this protocol, the technician was still found to be seronegative.

Given this incident, the hospital determined that ethically all individuals participating in the program were to have antibody studies drawn six weeks post-completion of the three dose protocol. The results of the post-screening revealed that only 65% of the participants had measurable antibody responses. The 35% who remained seronegative were offered a fourth dose of the vaccine. Of those individuals receiving the fourth dose, 78% remained seronegative.

In light of these facts (seroconversion results were well below the expected rates of 95-98% reported by the manufacturer in clinical trials), further vaccinations were curtailed until all variables could be assessed. Some of these included: the validity of vaccine studies, possible laboratory error, and the possible improper packaging and handling of vaccine.

Bipartisan laboratory analysis confirmed the results obtained at The Washington Hospital and a new shipment of the vaccine was provided by the manufacturer. At this writing (December, 1984), the program is proceeding but participating individuals have been advised of our study results and post-screening is included within the protocol. To date, the manufacturer has been unable to explain the discrepancy in our rate of seroconversion.

Those individuals presently participating in the Heptavax-B® protocol with the new vaccine lot will be post-screened six weeks following the third dose to determine their antibody status.

It should be noted that in communicating the results of The Washington Hospital to other area hospitals providing a Heptavax-B® vaccine pro-

*The manufacturer of Heptavax-B® vaccine is Merck Sharp & Dohme.
gram, it was found that their random post-vaccination screenings have also shown a low incidence of sero-conversion.

Most needle puncture protocols and known exposures to hepatitis B include screening (Anti-HBs) post-incident. This protocol at our institution and at other institutions also includes those individuals who have completed the Heptavax-B® program and assumed themselves to be immune. It was found that the number of non-seroconverters in this population is also appearing higher than that quoted by the manufacturer.

Summary

Hepatitis B is a major concern for health care workers. At CDC estimates, there are 400,000 to 800,000 asymptomatic carriers of the hepatitis B virus in the United States. The pool of these carriers is growing by 2-3% annually. The risk for contact with these carriers during clinical practice is ever increasing in light of more involved surgical procedures and transplant surgeries.

The advent of the hepatitis B vaccine (Heptavax-B®) has provided a possible answer. Many institutions are currently offering Heptavax-B® vaccine programs in an effort to protect those individuals at high risk of exposure to the hepatitis B virus.

Here at The Washington Hospital we are concerned with the discrepancy in our protocol results compared to those of the manufacturer and strongly suggest that all institutions and individuals who have received the hepatitis B vaccine consider post-screening. Since the results of our study have been made known, area hospitals are beginning to report similar results. Further studies need to be done to determine a more effective protocol.

Despite the results, the use of the vaccine is a major breakthrough in hepatitis B virus protection. However, the vaccine does not negate good techniques and appropriate precautions when dealing with the patient population.

Addendum

It would be appreciated that any additional data be shared. Please send information to the authors: The Washington Hospital, 155 Wilson Avenue, Washington, Pennsylvania 15301.

Update

According to a Merck, Sharp & Dohme spokesman, health care workers who do not develop antibodies after the standard three-dose protocol, could be provided with a fourth and fifth dose free of charge.*

REFERENCES


AUTHORS

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*Merck offers fourth and fifth doses of HBV vaccine to nonresponders. Hospital Employee Health, 1984. 3:149.