NEWLY LICENSED HEPATITIS B VACCINE

Robert J. Gerety

Office of Biologics
National Center for Drugs and Biologics
Food and Drug Administration
Bethesda, Maryland 20205

The recently licensed subunit hepatitis B vaccine (HEPTAVAX-B) is unique among vaccines in that it is manufactured solely from human plasma obtained from asymptomatic individuals with chronic hepatitis B. Plasma from donors selected for manufacturing this vaccine contains high concentrations of noninfectious hepatitis B surface antigen (HBsAg) particles and lower concentrations of infectious hepatitis B virus (HBV). The ratio of HBsAg to HBV can be as great as 10,000:1 (1). From the starting plasma, 22 nm spherical HBsAg particles are separated from HBV by ultracentrifugation. The 22 nm particles are then further purified by digestion with pepsin followed by the addition of 8M urea. Finally, the vaccine is treated with formaldehyde.

VACCINE PLASMA DONORS

Vaccine plasma donors are selected for their high titers of HBsAg. By federal regulation, they must be asymptomatic and in apparent good health (2). They must meet all federal requirements for acceptable plasmapheresis donors, except that their serum aminotransferase activity may exceed the level permitted normal donors (but it must be stable) (3). Each donor provides a complete history, receives a complete physical examination, and undergoes laboratory tests before his or her first plasma donation and must maintain normal levels of hemoglobin and serum protein and a normal hematocrit value throughout the course of plasma donations (2,3). In the general population, there are fewer than two acceptable (high titer) vaccine plasma donors among each 10,000 individuals.

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Among certain high-risk populations for hepatitis B, e.g. sexually active male homosexuals, there are approximately 80 acceptable vaccine plasma donors per 10,000 individuals.

VACCINE MANUFACTURE

To isolate the 22 nm noninfectious HBsAg particles, acceptable plasma pools are treated with ammonium sulfate (concentration step) followed by isopyknic ultracentrifugation in sodium bromide and rate zonal ultracentrifugation in sucrose. The purified 22 nm particles are then treated with pepsin (1 mg/L, pH 2.1 at 37°C for 18 hours) to digest residual plasma antigens, with 8M urea for four hours followed by dialysis, and with 1:4000 formaldehyde solution at 37°C for 72 hours (4).

VACCINE SAFETY

Ultracentrifugation of plasma to isolate noninfectious HBsAg particles has been shown to be capable of removing 10,000 infectious doses of HBV (1). Each of the three steps routinely applied during vaccine manufacture (pepsin, urea, and formaldehyde) has been individually shown to inactivate 100,000 infectious doses of HBV per milliliter by chimpanzee inoculation studies (5).

The procedures used in the manufacture of hepatitis B vaccine are also effective in inactivating viruses from every known group. The pepsin treatment has been shown to inactivate completely rhabdoviruses represented by vesicular stomatitis virus, poxviruses represented by vaccinia, togaviruses represented by sindbis, herpesviruses represented by herpes simplex (type 1), coronaviruses represented by infectious bronchitis virus, and reovirus (6,7). The urea treatment, in addition to inactivating all of the previously mentioned viruses, also has been shown to inactivate completely myxoviruses represented by Newcastle disease virus and picornaviruses represented by mengovirus (6,7); lesser concentrations of urea have been shown to inactivate viruses in the slow virus category represented by the scrapie agent (8). Formalin inactivates a wide variety of viruses, including parvoviruses, and has been recently shown in two separate studies to inactivate agents of human non-A, non-B hepatitis (9,10).

VACCINE TESTING AND EXPERIENCE

Each lot of licensed hepatitis B vaccine is injected into suckling and adult mice, guinea pigs, the allantoic and yolk sac of embryonated eggs, and into animal (Vero cells) and human-derived cell cultures (WI-38 cells) to confirm the absence of

infectious agents. In addition, a total of 22 doses of each vaccine lot are injected intravenously (i.v.) into chimpanzees that are examined for six months with weekly serum analyses and monthly liver biopsies. A total of more than 15 lots of the newly licensed hepatitis B vaccine has been tested in this manner, with no evidence of residual infectivity for hepatitis B or any other viral agent.

During clinical trials of the licensed vaccine involving 1900 vaccinees (11,12), only minor immediate reactions occurred. Complaints primarily concerned soreness at the injection site. To date, more than 19,000 persons have received this vaccine, including 8941 health care workers and 5985 healthy adults, children and infants who were not at high risk for acquiring hepatitis B; no serious reactions have been proven to be vaccine related so far (13).

ACQUIRED IMMUNE DEFICIENCY SYNDROME

The recognition of the acquired immune deficiency syndrome (AIDS) in previously healthy homosexual males, in Haitian immigrants to the United States, in addicts using drugs i.v., and in 84 heterosexual men and 34 women has led to speculation that an infectious agent may be responsible for this disorder. Acquired immune deficiency syndrome is recognized by the occurrence of either a life-threatening opportunistic infection (such as *Pneumocystis carinii*) or Kaposi's sarcoma in a person younger than 60 years who has no underlying immunosuppressive disease and has not received immunosuppressive therapy (14). Mortality from AIDS has ranged from 15% for those with Kaposi's sarcoma to 60% for those with *P. carinii* pneumonia (14)--far higher than the mortality seen from these disorders in patients without AIDS. Many patients with AIDS had a prodrome lasting weeks to months characterized by weight loss, lymphadenopathy, fever and diarrhea. Although this prodrome was more common in patients with *P. carinii* (14), it was by no means universal among patients with AIDS. It is not clear whether this prodromal lymphadenopathy reflects an immune dysfuncton predating the recognition of AIDS. In this regard, Kaposi's sarcoma in patients without AIDS may be associated with lymphoreticular neoplasms (15), suggesting that an immune defect may precede all cases of Kaposi's sarcoma.

ETIOLOGY OF AIDS

The etiology of AIDS is unknown. Suggested causes include single or repeated exposures to an unknown immunosuppressive agent or to a known agent, e.g. cytomegalovirus (14,16). Other suggested causes include exposures to antigenic substances, opiates (17),

nitrite inhalants (14), or chemotherapeutic agents to which homosexual males may be exposed during treatments for various disorders. The possibility of herpes simplex virus infection being a predisposing factor has not yet been discussed, although there is a high prevalence of infections by this agent among homosexual males and among patients with AIDS (18,19).

The recognition of cases of AIDS in heterosexual hemophilic patients, although in no way proved to be related to the life-saving blood-derived clotting factor concentrates that they receive, has raised questions regarding the safety of plasma donated for hepatitis B vaccine manufacture by persons with chronic hepatitis B who may have unrecognized or early AIDS. It is important that none of the hemophilic patients with AIDS described so far had received clotting factor concentrate from a common lot of product, despite having required frequent treatments (20) and despite the fact that these same lots had been infused into several hundred other hemophiliacs without resulting in AIDS. Also, a relatively small number of human viruses have been documented to be transmitted by blood (21), and, in some cases, these are "intracellular" viruses, e.g. cytomegalovirus, that are not thought to be transmitted by plasma. Active surveillance among hemophiliacs will continue to identify any additional AIDS cases in this group.

RISK-BENEFIT CONSIDERATIONS AND VACCINE USE POLICY

Although not convincingly documented to be transmitted by blood, AIDS does occur among populations that donate vaccine plasma. Since AIDS occurs among certain high-risk groups receiving the vaccine, it is inevitable that cases of AIDS will occur in vaccine recipients unrelated to the vaccine itself. There is little doubt that the licensed vaccine is highly effective in preventing hepatitis B (22). There are about 200,000 new cases of hepatitis B each year in the United States, 10,000 of these patients require hospitalization, up to 1000 die with fulminant hepatitis, and 10,000 to 20,000 experience chronic hepatitis B. It is estimated that half of these cases of hepatitis B can be prevented by immunizing all persons at high risk for hepatitis B with the licensed vaccine (22,23).

Despite the fact that a great body of data has not yet been accumulated from long-term evaluation of hepatitis B vaccine recipients, it is clear at this point that the known risk of hepatitis B for persons in high-risk groups far exceeds the risks of vaccine-induced infection by a theoretical transmissible agent that would have to survive the purification and inactivation procedures applied to the licensed hepatitis B vaccine. The recommendations of the Immunization Practices Advisory Committee

(23) have recently been reaffirmed (13); all persons at high risk for hepatitis B should receive hepatitis B vaccine.

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