The Status of Hepatitis Vaccines: Type A and Type B

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Abstract: The existence of five types of hepatitis viruses has been established until now, namely, hepatitis viruses A, B, C, D, and E. Among these, hepatitis viruses A, B, and C are of particular relevance in Japan. While vaccines are available against hepatitis A and B, none has as yet become available for hepatitis C. Both hepatitis A and B vaccines have satisfactory efficacy and minimal side effects. In particular, they are of great value in the prophylaxis of health care professionals against hepatitis A and B. The status of the hepatitis A and B vaccines is reported in this paper.

Key words: Hepatitis A vaccine; Hepatitis B vaccine

Hepatitis A Vaccine

1. Epidemiological background and the need for a vaccine

Hepatitis A virus (HAV) is transmitted by the fecal-oral route, through ingestion of contaminated drinking water or food, and proliferates mainly in the liver. The virus reaches the gastrointestinal tract via the bile, and is excreted in the feces, which then serves as a new source of infection.

Infection with the hepatitis A virus may occur in a sporadic fashion, in a small population (including intrafamily occurrence), or as a mass outbreak. The source of infection is usually untraceable in sporadic cases. Infection in a small population is often caused by contamination of food by the feces of patients with latent hepatitis who excrete HAV. To prevent such contamination, it is necessary for people who handle foodstuffs, such as cooks, to acquire the habit of routine and thorough hand washing. Mass outbreaks are often caused by contamination of drinking water or shellfishes (shellfishes concentrate HAV in their bodies, and were the cause of infection spreading among 200,000–300,000 people in Shanghai in 1987), or contamination of food in large food manufacturing companies, (contamination of strawberries in USA in 1997).

As a general prophylactic measure, it is important to avoid taking foods and drinks served under unheated conditions in HAV endemic regions (almost all countries excluding Japan, Scandinavia, and North America). However, it may not be realistic to specify the foods that must be avoided in high-prevalence areas.

It has been said that globally, hepatitis A...
outbreaks occur every 6–7 years. In Japan, outbreaks occurred in 1983 and 1990. Although an outbreak was expected in the year 1997, the annual incidence of hepatitis A has been decreasing steadily since the year 1990. In addition, there has been no conspicuous increase in the number of new patients diagnosed between the months of January and May, a pattern which was consistently noted in the previous years. The number of people infected with hepatitis A virus in previous years was estimated to be approximately 10,000 to 50,000 per year, but currently, the corresponding number runs into only several thousands. However, one cause for concern is the observation that the HE antibody prevalence curve is shifting steadily toward the elderly age group year by year, with a rapidly increasing susceptible population under the age of 50 years. Therefore, it is possible that once the spread of infection begins, a large epidemic outbreak may occur. Furthermore, Japanese people run the risk of becoming infected with the virus when they visit areas with high prevalence of hepatitis A.

The incidence of hepatitis A in Japanese people plotted by age shows a bimodal distribution, with two peaks at the age of 10 years and in the age range of 30 to 50 years. This suggests that intrafamily infection is dominant. This is also related to the fact that the duration of viremia, and thus the duration of viral shedding, is considerably longer than formerly expected, and that excretion of HAV continues even after the patient is cured of hepatitis. It would appear that this prolonged HAV excretion is responsible for maintaining HAV among humans.

2. Practical aspects of the HAV vaccine

HAV vaccine is a formalin-inactivated vaccine made from a strain of HAV attenuated in tissue culture. In Japan, the vaccine is a freeze-dried preparation different from, and superior to other foreign products, in that they contain no preservatives and adjuvants (immunopotentiators).

A phase-I clinical trial was begun in 1988, followed subsequently by phase II and phase III trials. The HAV vaccine was finally approved for use in October 1994. The results of all the trials were similar, both in terms of the efficacy
and in terms of the side effects of the vaccine. The HA antibody titer is considered to be maintained above the minimum protective level (10 mIU/ml) for more than 6 months when the vaccine is administered twice at the dose of 0.5 μg, at 0 and 2 or 4 weeks; protective titers have also been reported to be maintained almost throughout life when a third dose is administered in addition after 6 months. Fig. 1 shows a comparison of the antibody titers induced by three different inoculation schedules examined in a phase-II study. In this study, antibody production appeared to be easily induced by the vaccine, since most of the 1,500 subjects enrolled in the study became HA antibody-positive after the first inoculation, and all of the subjects became positive after the second inoculation. A ntibody induction showed a slight gender-related difference, but scarcely any age-related difference. A s to adverse reactions, pain, redness, and swelling at the injection site occurred in about 10% of the subjects, and general malaise and slight fever in about 3%.

3. Vaccination targets
Vaccination against hepatitis A is ideally recommended for all persons in the general population, because it has scarcely any side effects, the antibody is easily induced and protective titers are well maintained, and several people continue to excrete HAV for long periods of time after they become infected. O n a more practical level, the major candidates for vaccination include people traveling overseas to work, tourists on long vacations, persons in the vicinity of a source of intrafamily infection or a mass outbreak, cooks and food handlers, health care professionals, including nursing personnel, homosexuals (there are records of mass infection in this group both in Japan and overseas), and patients with advanced hepatic disease (who run the risk of developing hepatic failure).

Intramuscular injection of commercially available immunoglobulins has also been employed for prophylaxis against hepatitis A. H owever, since there are wide variations in the HA antibody content among preparations, it is impossible to predict the effective duration of the protection offered. Furthermore, since these are blood products, they should preferably be replaced by vaccines.

Hepatitis B Vaccine

1. Epidemiological background and the need for a vaccine
Hepatitis B virus (HBV) infection is transmitted by the following routes: 1) mother-to-child transmission; 2) sexual transmission; 3) infection via blood or blood products; 4) infection from injuries with instruments contaminated by the blood of patients with the infection.

In the case of mother-to-child transmission, almost 100% of the children born to mothers positive for the HBe antigen are infected with the virus, and 85% become HBV carriers. This is the major source of HBV carriers in Japan. O n the other hand, about 10% of children born to HBe antigen-negative mothers are infected with the virus; while these children rarely become carriers of the virus, they often develop fulminant hepatitis within 2–3 months after birth. Specific prophylactic measures against mother-child transmission of the infection will be described later. Since the program for preventing mother-to-child transmission of hepatitis B virus began in 1986, only 300–400 children per year have become carriers (0.05% of all infants born), which corresponds to only 1/10 of the number of carriers introduced into the population per year before the project began. F ulminant hepatitis among neonates has also become extremely rare.

Most cases of acute hepatitis B develop as a result of sexual transmission of the virus. T esting of the specific partner usually reveals that the person is an HBe antigen-positive HBV carrier. The incidence of acute hepatitis B exhibits a peak in people in their 20s, and varies in relation to the incidence of other sexually trans-
mitted diseases; there is a temporary decrease in the incidence after HIV has presented itself on the scene, and variations in the incidence became apparent within 3 months after HIV infection was first announced. Vaccination with the HB vaccine is extremely effective for preventing hepatitis B, but it is difficult to practice such prevention under the current circumstances.

Infection via blood or blood products has become extremely rare after the introduction of screening for the HBs antigen (1972) and HBC antibody (1989). Furthermore, performance of the nucleic acid test (NAT) on all blood materials has almost completely eliminated transmission of the disease by this route.

Transmission of infection via injury with instruments contaminated by blood from HBV carriers was relatively common when boiled syringes were used in medical practice. It has been estimated that the frequency of this form of transmission of the infection has decreased sharply since the 1970s when disposable syringes began to be used routinely. However, this mode of transmission of the infection is still prevalent among health care personnel.

2. Practical aspects of the HB vaccine

The most fundamental prophylactic measure against the spread of HBV infection is to increase the awareness in the general population that all body fluids, e.g., blood, can serve as a source of infection. When there is the possibility (high risk) that HBV infection may have occurred, passive prophylaxis using hepatitis B immunoglobulin (HBIG) (high-titer HBs antibody-containing immunoglobulin) in emergencies, or vaccination with HB vaccine in less urgent cases, are indicated. In particular, hepatitis B vaccination should be carried out in health care personnel, a high-risk population for HBV infection, especially those in the younger age groups, in whom antibody production is more strongly enhanced.

Although subcutaneous, intramuscular and intracutaneous routes are available for vaccination, the subcutaneous route is considered to be inferior to the intramuscular route.\(^8\) Intracutaneous inoculation yields a seroconversion rate comparable to that following intramuscular inoculation, even when the dose inoculated is only 1/5 of the intramuscular dose. However, the increase in antibody titer after intracutaneous inoculation is slightly less dramatic than that after intramuscular inoculation.

The standard vaccination schedule in Japan against hepatitis B consists of three inoculations at 0, 1, and 6 months. For the prevention of mother-to-child transmission, the vaccination is administered thrice, at 2, 3, and 5 months of age. It may be noteworthy that, usually, the third inoculation yields a better antibody response when it is carried out later than 6 months and within 12 months after the second inoculation, as long as there is no threat of fresh infection. However, it still remains to be precisely established as to how long after the second dose the third inoculation must be carried out. A third inoculation is, however, definitely recommended even if the timing of administration of the first and second doses of the vaccine is uncertain. Four inoculations at 0, 1, 2, and 12 months are also used overseas. Although this method is useful for rapid induction of the antibody, the third inoculation is not effective at yielding an increase in antibody titer in the long run. Where there is urgent need for antibody induction, e.g., in the prevention of mother-to-child transmission or in medical contamination accidents, inoculation thrice at 0, 1, and 3 months is practiced. It has been reported that early seroconversion can be achieved by administration of the vaccine thrice at shorter intervals, i.e., 1-week intervals.

In Japan, vaccination for the prevention of mother-to-child transmission is, as a rule, begun at 2 months after birth, since it has been reported that a delayed start yields better results in neonates who exhibit weak immune responses, considering the relatively low potency of the plasma-derived vaccine that was used at the time that the project for preventing the transmission of the infection was initiated.
Now that recombinant vaccines with higher potency are available, the first inoculation immediately after birth, as in countries overseas, may be a feasible option.

3. Side effects of the HB vaccine

As side effects, transient slight fever, muscle aches, local changes, or general malaise were seen in about 10% of the inoculated individuals for several days after the inoculation. Eruptions due to yeast allergy may occur very rarely as a prominent adverse reaction, which has been confirmed by re-administration and other tests. Summed data on the side effects in a large number of vaccinated individuals have been reported by McMahon et al. 9)

Conclusion

Currently, vaccines for hepatitis A and B are commercially available. Both are highly effective and have minimal side effects.

Although the incidence of hepatitis A has been decreasing in recent years, it is difficult to predict when a mass outbreak might occur. Groups which are candidates for HA vaccine inoculation include health care personnel, cooks and food handlers, homosexuals, persons traveling overseas, etc.

On the other hand, HB vaccine should be administered to health care personnel, especially those in the younger age groups in whom stronger induction of antibody is likely. Meticulous prevention of mother-to-child transmission must be continued for 2 to 3 decades to completely eliminate HBV infection in Japan. In addition, acute hepatitis B should be addressed as a sexually transmitted infection.

REFERENCES