DRAFT

MILES

Memorandum

Cutter Biological

Berkeley, CA

Date June 21, 1989

Subject **Factor VII Concentrates and the Relative Risk of Transmitting Hepatitis B**

From R. Rousell

To C. Moore

Every Factor VIII concentrate manufactured from human blood plasma carries the potential risk of transmitting hepatitis B. This is irrespective of the precautions used to eliminate hepatitis B positive units from the donor pool and irrespective of the procedures used to inactivate viruses (dry heat treatment, heating in solution/pasteurization, steam heating, chemical inactivation methods). It is evidenced by the fact that the package insert for EVERY Factor VIII concentrate licensed in the USA carries a warning stating that the presence of hepatitis viruses must be assumed in every Factor VIII concentrate. The available test methods are not sufficiently sensitive to detect all units of potentially infectious plasma, nor are the viral inactivation methods used, totally effective in eliminating viral infectivity. The procedures adopted have, however, markedly reduced the infection risk so that today only isolated lots are capable of transmitting hepatitis B in sharp contrast with the situation in the early 1970s prior to the development of specific and sensitive assays for hepatitis B and to the subsequent development of the various methods of viral inactivation. At that time, the frequency of contamination of lots of Factor VIII concentrates was such, that exposure to hepatitis B was considered invariable in all severe hemophiliacs prior to adolescence, provided they were receiving regular therapy with a Factor VIII concentrate. By the late 1970s exposure to non-A, non-B hepatitis had at least equaled that of exposure to hepatitis B. Thus, prior to the introduction of the virally inactivated preparations, over 90% of severe hemophilics treated with coagulation factors were considered to have been exposed to hepatitis B as well as non-A, non-B hepatitis.

The introduction in the USA, and in many other countries throughout the world, in the early 1980s of a safe and effective vaccine for immunization against hepatitis B was another milestone in eliminating transmission of hepatitis B by coagulation concentrates. Today, active immunization against hepatitis B is recommended by experts world-wide as standard therapy in the management of patients with hemophilia, such immunization being performed as early as possible.

On April 24, 1989, Cutter USA received a report from Japan, of two cases of hepatitis B occurring in patients with severe hemophilia B who had received Koate-HS. On May 30, 1989 we were informed of a third case. These reports deserve further comment.

The incubation period for hepatitis B (period from time of exposure to time of onset of symptoms) varies between four weeks and six months, with an isolated, occasional delays of even up to one year. The first serological evidence (positive HB_sAg) occurs two weeks to two months prior to onset of symptoms. Serum transaminase levels rise at about the time of onset of symptoms and anti-HB_c also becomes detectable. Anti-HB_c can persist for a few months to several years, while HB_sAg may remain positive for a few days to two or three months or even become persistent in a chronic carrier state. Late in convalescence, antibody to HB_sAg appears. In the USA and Western Europe, about 10% of the population are HB_sAb positive while less than 1% are HB_sAg positive (the figures for the countries of the Far East are considerably higher).

Case 1. Tachikawa, 13 year old, hemophilia A.
Received Conco-eight HT November 24, 1988. Lot number not known.
Received Koate-HS December 19, 1988; December 23 to 29, 1988;
January 10, 1989; January 18, 1989;
January 23 to 30, 1989
Koate-HS lots 60F 036 and 60F 038.

March 13, 1989 Clinical Hepatitis.
March 20, 1989 Positive HB_sAg, HB_eAg, HB_eAb, HB_cAb (IgM)

Comment

Given an incubation period of four weeks to six months, this patient may have been exposed any time from between mid-September 1988 to mid-February, 1989. During this period he received one lot of Conco-eight (lot number unknown) and two lots of Koate-HS. (Lot numbers 60F 036 and 60F 038). It is not known if the Conco-eight-HT was wet or dry heated. It is established that wet heating is superior, as regards viral inactivation, than dry heating. No other risk factors could be elicited. Thus it must be concluded that the probable source of hepatitis B infection is one of the Factor VIII concentrates. The fact that two lots of Koate-HS were used, and probably only one of Conco-eight-HT, would increase the risk from Koate-HS. However, if the Conco-eight was dry heated, then the risk from Conco-eight becomes greater. The number of lots used is most important in defining the relative risk, while the actual number of units given is of far less significance. In summary therefore, it appears that the hepatitis B was probably transmitted by one of the concentrates, but it is impossible to define which one or to apportion any blame.

Case 2. Himeji, 1 year old, severe hemophilia A.

Conco-eight: HT Lots L135, L138 and L140 between December 1987 and December 1988. (Dry heated prior to October 5, 1988).
Koate HS: Lots 60F 009, 60F 036 and 60F 038 between December 24, 1988 and April 18, 1989

Comment

The patient was HB_sAg negative in November 1988 but by April 8, 1989, had become HB_sAg positive, and was also positive for HB_eAg and HB_cAb. This confirms the diagnosis of recent hepatitis B infection. There is a single elevated level of SGPT recorded on November 26, 1988 (144 units). This level is well over twice the highest level ever previously measured in this subject. The question is, did the single elevation observed in late November 1988 indicate an acute hepatitis occurring about that time, even though the assay for HB_sAg was negative? Again, it is probable that the hepatitis was transmitted by one of the coagulation concentrates administered; it is not possible to apportion the blame.

Case 3. Iwata, 4 years old, severe hemophilia A.
This case is more complex having received dry heated and wet heated lots of both Conco-eight and Koate. Details of the lots of Conco-eight used are not available, but the product was used until June 1988.
Between June and September 27, 1988, Koate-HT was given.
After September 27, 1988, through May 1989, Koate-HS was given. Lots 60F 009 and 60F 036 were used.

Comment

In May 1988, while receiving Conco eight (dry heat), the patient developed non-A, non-B hepatitis.

In March 1989, the subject was given Hepatitis B vaccine (Bimmugen). By mid-May the patient had developed clinical signs and was becoming jaundiced. He was found positive for HB_sAg and HB_cAb (IgM), but negative for HAAb (IgM). Acute hepatitis B was thus confirmed.

The subject was actively immunized against hepatitis B in March 1989. Could the vaccine have transmitted active hepatitis B? If this possibility is eliminated, then it would seem logical that the subject was already incubating hepatitis B at the time of immunization, in which case the vaccine would not prevent the development of hepatitis B. A satisfactory vaccine will already confer immunity in over 40% of cases within one month of the first injection. If the subject was already infected with hepatitis B in March 1989, then infection could have occurred any time between October 1988 and February 1989. It is rather surprising that Conco-eight transmitted non-A, non-B hepatitis in May 1988 but not hepatitis B. However, the subject remained hepatitis B surface antigen negative until May 1989. Provided other forms of non-parenteral transmission of hepatitis B--especially the use of the vaccine--are eliminated, it is possible that the hepatitis B was transmitted either by Koate-HT or Koate-HS. The risk of transmission by Koate-HT is greater than for Koate-HS. However, the incubation period in this particular subject would seem to implicate Koate-HS more than Koate-HT. In summary, the possibility of transmission of hepatitis by the vaccine must be eliminated. If this can be done, then it is possible that either Koate-HT or Koate-HS could have transmitted hepatitis B.

Summary

In spite of all precautions undertaken in the manufacture of coagulation concentrates, all preparations still carry a risk of transmitting hepatitis. Good medical practice in the management of patients with hemophilia recommends active immunization, against hepatitis B, be undertaken as early in life as possible. The details of the three cases of hepatitis B reported from Japan are such that no specific product can be implicated as being the cause of hepatitis B. In the follow-up and investigation of such cases, it is of utmost importance to have access to very accurate hospital records. The dates of administration of each lot of coagulation concentrate from every manufacturer are essential. Such records should be taken back for at least one year prior to the confirmation of hepatitis B, because as stated previously, while the incubation period for hepatitis B is usually four weeks to six months, periods of up to one year have been recorded.

RHR:jh

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