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Epidemiologic Notes and Reports Non-A, Non-B Hepatitis Associated with a Factor IX Complex Infused During Cardiovascular Surgery -- Arizona

On June 14, 1985, the Division of Disease Control Services, Arizona Department of Health Services, was notified by infection-control personnel at a local hospital of 13 cases of non-A, non-B hepatitis among patients who had undergone cardiovascular surgery at the hospital during the preceding 6 months. All the patients had received factor IX complex produced by Alpha Therapeutic Corporation (Brand B) because of bleeding during their surgery.

A systematic review of pharmacy records for 1984 and 1985 determined factor IX complex usage patterns. Between January 1, 1984, and June 3, 1985, 172 patients had received factor IX complex during cardiovascular surgery (81 Brand A; 90 Brand B; one Brand C). Brand B factor IX complex was added to the hospital pharmacy in October 1984.

Cases were identified through questionnaires distributed to all physicians involved with the care of three groups: the cohort of Brand A factor IX complex recipients who survived more than 2 weeks following surgery, the cohort of Brand B factor IX recipients who survived more than 2 weeks, and a sample from the cohort of 1,625 cardiovascular patients who received no factor IX complex during surgery and survived more than 2 weeks (matched to the Brand B group for age, sex, type of operation, and date of surgery within 1 month). Completed information was received for 55 (74%) of 74 Brand A factor IX complex recipients, 64 (85%) of 75 Brand B factor IX complex recipients, and 59 (79%) of 75 in the matched nonrecipient sample.

A case of postsurgical non-A, non-B hepatitis was defined as a patient who developed an illness with a discrete date of onset following surgery and characterized by: (1) jaundice and/or elevated serum aminotransferase (ALT) levels greater than 2 1/2 times the upper limit of normal, lasting at least 1 week; (2) negative serologic tests for IgM hepatitis A virus antibody (anti-HAV) and hepatitis B surface antigen (HBsAg) during illness; (3) no evidence of underlying liver disease or recent history of hepatotoxic drugs in dosages likely to produce liver dysfunction. A probable case was defined as above, but with no or incomplete serologic testing for markers of viral hepatitis.

The investigation identified 23 cases and seven probable cases of non-A, non-B hepatitis; 27 were among Brand B factor IX complex recipients, and three were among Brand A factor IX recipients (Figure 1). The most commonly observed symptoms were: fatigue (85%), anorexia (81%), nausea and/or vomiting (59%), dark urine (52%), light stools (41%), and abdominal pains (37%); 19 (63%) were jaundiced, including 17 Brand B factor IX recipients

and two Brand A factor IX recipients. Liver function tests showed median peak ALT of 801.5 IU (range 153-2,824) and bilirubin 5.3 mg/dl (range 0.4-22.9 mg/dl). Six (22%) patients required rehospitalization because of hepatitis-related symptoms; one patient died, with non-A, non-B hepatitis reported as a contributing cause of death. The incubation period for cases among Brand B factor IX complex recipients was a median of 7 weeks (range 2-17 weeks) from the date of transfusion to the onset of symptoms; for Brand A, the incubation period was a median of 15 weeks (range 1-19 weeks). Peak elevations in serum transaminases occurred a median of 9 weeks from the date of transfusion.

The attack rate for Brand B factor IX complex recipients was 42% (27/64), significantly higher than the 5% (3/55) attack rate for Brand A recipients (relative risk = 7.7, p 2 x 10))-5))) or the 0% (0/59) in nonrecipients (p 1 x 10))-6))). The difference in attack rates between Brand A factor IX complex recipients and nonrecipients was not statistically significant (p 0.05).

The attack rate for Brand B recipients was about 40%, and that for nonrecipients of factor IX was 0%, irrespective of quantity of other blood products (Table 1). A similar comparison of Brand B to Brand A factor IX recipients showed no differences in receipt of other blood products; a stepwise multiple regression analysis of all factor IX recipients showed that receiving Brand B factor IX was the only risk factor significantly associated with hepatitis (p 0.0001).

Units of Brand B factor IX complex given to surgery patients came from five different lots. Each lot was associated with cases and probable cases. Attack rates for single-lot recipients ranged from 14% to 100% (Table 2). Reported by D Matthews, R Harmon, MD, Maricopa County Div of Public Health, SJ Englender, MD, LF Novick, MD, Director, GG Caldwell, MD, State Epidemiologist, Arizona Dept of Health Svcs; Div of Field Svcs, Epidemiology Program Office, Hepatitis Br, Div of Viral Diseases, Center for Infectious Diseases, CDC.

Editorial Note

Editorial Note: Clotting factor preparations have frequently been linked to the transmission of non-A, non-B hepatitis (1,2). These products are prepared from pooled plasma from multiple donors. Inoculation of nonheat-treated products into susceptible animals (chimpanzees) is associated with development of non-A, non-B hepatitis. In hemophilia patients who routinely receive commercial factor preparations, episodes of non-A, non-B hepatitis are common, and as many as 50% may develop signs of chronic liver disease, probably due to non-A, non-B infections. Studies in first-exposed hemophilia patients and in surgery patients who receive clotting factor preparations suggest the risk of non-A, non-B hepatitis in these patients may be close to 100% (3,4). Heat treatment of clotting factor products was initiated at about the time of the outbreak; however, none of the products used in this outbreak received heat treatment. While all factor IX complex and antihemophilic factor preparations are now treated to reduce the risk of viral disease transmission, the methods currently used do not appear to inactivate the causative agents of non-A, non-B hepatitis (5,6).

Non-A, non-B hepatitis in the United States is probably caused by at least two different viral agents (1,7). Because of difficulty in conclusively identifying the causative agents and developing serologic tests, it remains a diagnosis of exclusion. Epidemiologic studies indicate that percutaneous or bloodborne transmission routes predominate, with 20% of affected persons acquiring infection by blood transfusion, and 15%, by percutaneous drug abuse. Furthermore, non-A, non-B hepatitis now causes 80%-90% of the post-transfusion hepatitis observed in this country. Previously, outbreaks have been described in hemodialysis units (8) and plasmapheresis programs (9).

Non-A, non-B hepatitis associated with clotting factor preparations has been reported to be variable in clinical presentation, usually clinically milder with less icterus than other types of non-A, non-B hepatitis (10). The reasons for the severity of illnesses reported in this outbreak are not known. However, it could be due to either a different viral agent contaminating the clotting factor complex than that in previously reported outbreaks, to higher doses of the infectious organism, or to host-factor differences. The reasons for significantly different risks of illness associated with the products of different commercial manufacturers is also not known but possibly relates to differences in manufacturing processes or to differences in the donor pool that contributed to the respective products.

Because of the high risk of viral hepatitis, recommended use of clotting factor products has been limited to persons with known clotting factor deficiencies. In other settings, single-donor products carry a lower risk and are preferable. At least two outbreaks of non-A, non-B hepatitis have now been reported in surgery patients treated with clotting factor preparations (4). Prevention of non-A, non-B hepatitis in this population clearly depends on physicians adhering to strict indications for the use of clotting factor preparations and avoiding these products when at all possible.

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