Post-Konyne Hepatitis:

The Ineffectiveness of Screening for the Hepatitis B Antigen (HBAg)

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Sixteen patients who received Konyne for bleeding episodes or for hemostasis during surgical procedures were evaluated for signs of posttransfusion hepatitis. Four patients died from their primary disease. Of the remaining 12 patients at risk, six patients developed posttransfusion hepatitis. Sera from four of the six patients with hepatitis were positive for the hepatitis B antigen (HBAg). Aliquots of Konyne from the specific lot (K4797) implicated in three cases of HBAg-positive hepatitis were negative for HBAg by immunodiffusion, immunoelectroosmophoresis, and radioimmunoassay. The high incidence of hepatitis associated with Konyne considerably limits the use for this specialized coagulation factor concentrate. HBAg screening by available technics does not necessarily detect Konyne preparations capable of transmitting HBAg-positive hepatitis.

BETWEEN July 1969 and May 1971, 15 patients with acquired hypoprothrombinemia and one patient with hemophilia B were treated with Konyne* for the management of bleeding episodes or for hemostasis during surgical procedures.

The study was initiated following reports of successful therapy with similar prothrombin complex concentrates in patients with acquired hypoprothrombinemic bleeding disorders, including hepatic insufficiency and sodium warfarin overdosage.[14, 16, 17] However, our failure to document significant hemostatic benefit in patients with acquired hypoprothrombinemia associated with liver disease,[12] as well as early reports of post-Konyne hepatitis from other institutions,[2, 4, 6-8] resulted in our subsequent restriction of this specialized plasma fraction to patients with congenital coagulation factor deficiencies.

All patients receiving Konyne who survived their acute illnesses were followed up at regular intervals for clinical and laboratory signs of posttransfusion hepatitis. When a specific production lot (K4797) of Konyne became implicated in three cases of hepatitis B, unused vials from this lot were quarantined. Aliquots were submitted for hepatitis B antigen (HBAg) testing to determine whether the infectivity of this lot could be detected by the most sensitive methods available.

Materials and Methods

All patients receiving Konyne were seen in consultation by the Hematology Service Georgetown University Hospital for the management

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* Human factor IX complex produced by Cutter Laboratories, Berkeley, California.

TABLE 1. *Case Studies*

Patient	Diagnosis	Indication	Konyne No. of Vials	Konyne Lot No.	Hepatitis Follow-Up
C.L.	Cirrhosis	Incisional oozing	2	K4189	Died
H.N.	Cirrhosis	Incisional oozing	3	K4189	Died
A.L.	Cirrhosis	Upper G.I. hemorrhage	2	K4189	Died
N.B.	Cirrhosis	Upper G.I. hemorrhage	3	K5925	Died
S.H.	Chronic active hepatitis	Liver biopsy	3	K4189	No hepatitis
G.H.	Cirrhosis	Renal biopsy	2	K4189	No hepatitis
R.H.	Cirrhosis	Liver biopsy	2	K4127	No hepatitis
J.L.	Coumadin overdose	Intracerebral hemorrhage	2	K4189	No hepatitis
H.D.	Coumadin overdose	Retrotracheal hematoma	2	K4189	No hepatitis
M.Bl.	Coumadin overdose	Upper G.I. hemorrhage	2	K4797	No hepatitis
M.Ba.	Coumadin overdose	Retroperitoneal hemorrhage	2	K4797	HBAg-positive hepatitis
N.D.	Cirrhosis	G.I. hemorrhage	1	K4797	HBAg-positive hepatitis
D.L.	Hemophilia B	Dental extraction	4*	K4797	HBAg-positive hepatitis
N.C.	Cirrhosis	Peptic ulcer	2*	K5925	HBAg-positive hepatitis
R.C.	Cirrhosis	G.I. hemorrhage	2	K4127	HBAg-nonreactive hepatitis
H.B.	Cirrhosis	Liver biopsy	2	K5925	HBAg-nonreactive hepatitis

* Also received 5 units of FFP prescreened to be HBAg-nonreactive.

of hypoprothrombinemia associated with life-threatening bleeding episodes or in preparation for surgical procedures (Table 1). Konyne was administered after documentation of specific coagulation factor deficiencies within the prothrombin complex (factors II, VII, IX, and X).[12] Ten patients had Laennec's cirrhosis documented by liver biopsy or subsequently at postmortem. One patient had chronic active hepatitis documented by liver biopsy and four patients had acute hemorrhagic complications from Coumadin-induced hypoprothrombinemia. One patient with hemophilia B received Konyne in preparation for dental extractions. Except for two patients (N.C., D.L.) who each received five units of single donor fresh frozen plasma (FFP), prescreened to be HBAg-nonreactive by immunoelectroosmophoresis (IEOP), no other patient received additional blood products during the study.

All surviving patients were evaluated for clinical and laboratory signs of posttransfusion hepatitis at four to eight week intervals for a minimum of 15 months after receiving Konyne. Physical examinations were recorded as well as serial SGOT/PT, LDH, alkaline phosphatase, and bilirubin determinations. Specimens of patients' sera frozen prior to Konyne infusions and fresh sera obtained at four to eight week intervals after Konyne were tested for HBAg by IEOP.

Testing for HBAg (hepatitis associated antigen, HAA) and for hepatitis B antibody (HBAb, anti-HAA) was performed on undiluted aliquots of Konyne by microimmunodiffusion[10] and macro-Ouchterlony[3] technics. IEOP was used to test undiluted and serially diluted (1:2-1:512) aliquots.[11] Radioimmunoassay (RIA) was performed by the method of Ling and Overby, as described by Ginsberg

et al.[5] Aliquots with and without the addition of goat anti-HBAg were pelleted at 25,000 *g* and submitted for electron microscopy and negative staining.[15]

Results

Four patients died from complications of their primary illnesses before the risk of post-Konyne hepatitis could be evaluated. Six of the remaining 12 patients developed clinical and laboratory signs diagnostic of posttransfusion hepatitis (range 2.0-7.0 months). Their clinical and laboratory findings consisted of jaundice, hyperbilirubinemia, bilirubinuria, and marked elevations of SGOT/SGPT and LDH. Sera from four of the six patients with hepatitis were positive for HBAg by IEOP during the early phase of the illness and became negative during the convalescent phase. Two of the patients who developed HBAg-positive hepatitis (M.Ba., N.D.) had received only Konyne from lot K4797. The remaining two patients who developed HBAg-positive hepatitis (N.C., D.L.) had each received five units of FFP in addition to Konyne. All FFP had been prescreened by IEOP to be HBAg-nonreactive. Only one (M.Bl.) of the six patients who did not develop posttransfusion hepatitis had received Konyne from lot K4797.

Aliquots of Konyne from lot K4797 were nonreactive for HBAg and HBAb by microimmunodiffusion, macro-Ouchterlony, and IEOP. Similarly, HBAg was not detected in the Konyne aliquots by RIA. Two additional lots of Konyne (K6209 and K6533) were also nonreactive for HBAg by radioimmunoassay, but none of the patients in the present study received Konyne from these lots. Electron microscopy did not detect 20 nm, tubular, or 42 nm (Dane) virus-like particles, although control sera from patients with HBAg-positive hepatitis had abundant spherical and tubular particles.

Discussion

The finding of post-Konyne hepatitis in six of 12 patients at risk is consistent with that of others reporting an incidence of 40[2] to 67 per cent.[4, 9] Although HBAg reactivity at low titers in Cohn fractions used in the production of Konyne have been reported,[13] we are not aware of reports correlating negative HBAg testing of Konyne with cases of HBAg-positive hepatitis. The availability of unused vials of a production lot of Konyne (K4797), known to transmit HBAg-positive hepatitis, provided us with the opportunity of determining whether the infectivity of this lot could be detected by the most sensitive screening methods available. Our findings indicate that although the immunologic and ultrastructural characteristics generally thought to be associated with hepatitis infectivity in plasma were absent from the Konyne preparation, the material was fully capable of transmitting HBAg-positive hepatitis. This suggests that the infectious agent was present, but was not detected by the most sensitive tests available. As recent work suggests,[1] the etiologic agent of hepatitis B, or some infectious subunit of it, may be antigenically unrelated to HBAg. We conclude that HBAg testing of Konyne by available methods does not necessarily detect preparations capable of transmitting HBA-g positive hepatitis.

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