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Commercial factor VIII associated hepatitis, 1974–75, in the United Kingdom: a retrospective survey

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SUMMARY

A retrospective survey of transfusion hepatitis associated with a brand of commercial Factor VIII was carried out in 24 Haemophilia Centres from January 1974 until December 1975. Of 371 patients who were transfused with this product, and were followed up, 78 cases of hepatitis affecting 66 patients were found (17·7 %). Two types of hepatitis were observed: hepatitis B and non-B hepatitis, the latter with an incubation period of between 8 and 60 days. Twelve patients contracted two types of hepatitis, non-B followed by hepatitis B. Only one patient died after contracting hepatitis B. Four of the suspect batches of concentrate were found to be positive for HB_sAg by radioimmunoassay.

There was evidence that the presence of hepatitis B surface antibody in a patient's serum prior to exposure was associated with immunity to hepatitis B. Evidence was presented suggesting that the non-B hepatitis observed was not due to hepatitis A. The factors affecting the incidence of transfusion hepatitis in haemophiliacs were discussed.

INTRODUCTION

As a result of the occurrence of an outbreak of hepatitis at the Bournemouth Haemophilia Centre, associated with the first use of a commercial brand of Factor VIII (Brand 'L') replacement therapy in 1974 (Craske, Dilling & Stern, 1975), we decided to conduct a retrospective survey of the use of this product in British Haemophilia Centres with the aim of finding out if there was a similar incidence of hepatitis associated with its use elsewhere. Directors of Haemophilia Centres participating in the survey were asked to report the clinical details of cases of hepatitis possibly associated with transfusions of Brand 'L' to the Oxford Haemophilia Centre, using a standardized sickness record form. Information was also sought of all patients who were transfused with suspect batches and did not contract hepatitis. Details were also obtained of the transfusion histories of cases for the 6 months prior to the onset of hepatitis.

DEFINITION OF HEPATITIS

Only patients with symptoms and signs compatible with a diagnosis of hepatitis were included in the survey. A patient was considered to be suffering from hepatitis when three or more symptoms or signs compatible with a diagnosis of hepatitis were present as indicated on the sickness record form together with evidence of abnormal liver function tests. These were considered abnormal when a figure of at least twice the upper limit of normal serum aspartic or alanine aminotransferase, or both, as obtained by the local hospital biochemistry laboratory, was present within 3 weeks of the onset of symptoms. A serum bilirubin was considered abnormal if a figure of at least twice the upper limit of normal was obtained on the same occasion.

Cases of hepatitis were classified as 'B' or 'non-B'. Hepatitis B was considered to be present when the serum was positive for hepatitis B surface antigen (HB_sAg) by reverse passive haemagglutination (RPHA) or electrophoresis (Craske *et al.* 1975) within 1 month of the onset of symptoms. The same patient should previously have been HB_sAg negative and hepatitis B surface antibody (anti-HB_s) negative. Non-B hepatitis was considered present when all serum specimens from a patient with acute hepatitis were negative for HB_sAg as defined above.

For symptomless hepatitis B infections either a positive test for HB_sAg or seroconversion to anti-HB_s positive by passive haemagglutination (PHA) and hepatitis B core antibody (anti-HB_c) by electrophoresis was considered to be evidence of recent hepatitis B infection.

LABORATORY TESTS

Tests for HB_sAg were performed by RPHA (Chrystie, Islam, Banatvala & Cayzer, 1974) and electrophoresis as previously described (Craske *et al.* 1975). Anti-HB_s was estimated by PHA (Vyas & Shulman, 1970) using a commercial test kit supplied by Electro Nucleonics Inc. Tests for anti-HB_c were done by immunoelectro-osmophoresis (IEOP) according to a modification of the method described by Pesendorfer, Krassnitsky & Wewalka (1970) using HB_cAg prepared from post-mortem liver obtained from a carrier of HB_sAg who had received immunosuppressive treatment. Tests for HB_sAg on suspect batches of Factor VIII concentrate were kindly performed by Dr D. S. Dane of the Middlesex Hospital Medical School using a solid phase radioimmunoassay (RIA) sandwich technique (Heathcote, Cameron & Dane, 1974). RIA tests for Anti-HB_s were performed using the Ausab RIA technique (Abbott Laboratories Inc.).

Specimens of serum were obtained from the virus laboratories responsible for testing for HB_sAg which received sera from patients who had received transfusions of Brand 'L'. A study of the incidence of symptomless hepatitis B infections was possible only at Bournemouth and Alton, as sera were obtained before and after the hepatitis outbreak as part of a surveillance programme of the incidence of transfusion hepatitis (Craske *et al.* 1975; Y. E. Cossart & S. G. Rainsford, personal communication). A few patients with symptomless hepatitis B were detected by chance elsewhere when they became positive for HB_sAg.

Table 1. *Factor VIII associated hepatitis: number of cases in relation to severity of haemophilia*

Haemophilia disease state	Cases: non-B hepatitis	Hepatitis B	2 attacks (non-B + B)	Total transfused
(A) Severe (VIII = < 2 %)	25 (9·8)	18 (7·0)	6 (2·3)	253†
(B) Mild (VIII = > 2 %)	7 (14·5)	5 (10·4)	3 (6·2)	48
(A*) Severe c̄ VIII inhibitors	9 (22·5)	1 (2·5)	1 (2·5)	40
Von Willebrand's disease	2 (50·0)	1 (25·0)	0	4
Haemophilia carriers	0	1 (50·0)	0	2
Christmas disease (IX) deficiency	0	1	0	1
Disease state unknown (all haemophiliacs)	5 (21·7)	3 (13·0)	2 (8·6)	23
Total	48 (12·9)	30 (8·0)	12 (3·2)	371

Total, one or more attacks of hepatitis = 66 (17·7)
Figures in parentheses indicate percentages.
† Three patients transfused but died of other causes; not included.

RESULTS

Returns were received from 24 Haemophilia Centres: 374 patients received transfusions of one or more batches of Brand 'L' over the period. Three patients died from illnesses not related to transfusion hepatitis, and were therefore excluded from this survey. Patients were classified according to the severity of their disease; A = less than 2 % Factor VIII activity, B = > 2 %, A* indicated less than 2 % with the presence of Factor VIII inhibitors.

The distribution of patients according to this classification and the occurrence of cases of hepatitis is shown in Table 1. Four patients with Von Willebrand's disease, two carriers of the haemophilia gene and one patient with Christmas disease also received a transfusion of Brand 'L'. A large proportion of patients who received Brand 'L' had severe haemophilia.

Hepatitis

Two types of hepatitis were observed.

(1) A short incubation (8–60 days) non-B hepatitis clinically identical with hepatitis A.

(2) Hepatitis B, with incubation periods from 50–185 days.

Of 371 patients transfused, a total of 78 cases of hepatitis affecting 66 patients (17·7 %) were considered to have been associated with transfusions of Brand 'L'. Of these 48 were non-B and 30 hepatitis B, of which 4 were symptomless, having HB_s antigenemia with no overt hepatitis. Twelve patients contracted 2 attacks of hepatitis; non-B followed by hepatitis B. A further 3 cases of non-B and 3 of hepatitis B were also reported but were considered to have been due to transfusions of other therapeutic material and 3 other cases of jaundice were excluded from the survey as there was insufficient information available.

Table 2. *Alton: association of short incubation hepatitis with a previous transfusion of batches T and U*

	T and U	No T and U	Total
Hepatitis	8	0	8
No hepatitis	14	22	36
Total	22	22	44

Evidence for Brand 'L' as a cause of hepatitis

This rests on the following lines of evidence.

(1) The occurrence of 6 cases of non-B hepatitis and 6 of hepatitis B in patients transfused only with the suspect batches of Brand 'L' during the previous 6 months for hepatitis B and 3 months for non-B hepatitis, before the onset of their illnesses.

(2) The occurrence of clusters of cases of hepatitis after the use of Brand 'L' for the first time. At Bournemouth no cases of jaundice occurred in the year preceding the first use of Brand 'L', whereas 6 cases of jaundice were observed during the 6 months after its introduction (Craske *et al.* 1975). At Alton 4 cases of non-B hepatitis occurred between 1970 and 1974 (Y. E. Cossart & S. G. Rainsford, personal communication). In 1974, 8 cases of non-B hepatitis were observed after the introduction of Brand 'L'. The association of this hepatitis with a transfusion of 2 batches of Brand 'L', 'T' and 'U', is shown in Table 2. Two of the patients who had non-B hepatitis subsequently developed hepatitis B.

(3) With the exception of 1 case of non-B hepatitis and 1 of hepatitis B, all cases of hepatitis reported in this survey occurred within 6 months of the affected patient receiving his first transfusion of Brand 'L'. This phenomenon has been observed on a previous occasion (Kasper & Kipnis, 1972). The reasons for the prolonged incubation periods in these 2 cases are not known. Both patients received only transfusions over this period of batches of Brand 'L' known to be associated with the occurrence of hepatitis, and there were no other known sources of infection in these patients.

(4) The original concentrates of 4 of the 6 batches associated with cases of hepatitis B were positive for HB_sAg by a solid phase radioimmunoassay (RIA) test (Heathcote *et al.* 1974).

Non-B hepatitis

Of the 43 cases 7 were anicteric. Most were clinically mild, the patients recovering within 1 month. One patient died in the acute phase of illness, but probably from causes not related to his jaundice. A second patient had a moderately severe illness lasting 6 weeks and then recovered. A third patient at Alton had evidence of chronic liver dysfunction 2 years after his attack of hepatitis. Before this his alanine aminotransferase was normal. There was no difference between the incubation periods of icteric and non-icteric cases.

Table 3. *Factor VIII associated hepatitis B: clinical features*

Batch implicated	Total cases	With symptoms		Without symptoms HB_sAg pos. only	Seroconversion HB_sAB, HB_cAB Bournemouth, Alton only
		Icteric	Anicteric		
P	0	—	—	—	—
Q	3	2	1	0	1
R	7	5	2	0	1
S	7	6	0	1	4
T	5	3	2	0	0
U	3	2	0	1	1
V	5	3	0	2	0
Total	30	21	5	4	7

Table 4. *Factor VIII associated hepatitis B: clinical symptoms related to age*

	Years					Age unknown	Total
	<10	11–20	21–30	31–40	40+		
With symptoms	7	5	3	6	3	2	26
Without symptoms	3	5	0	0	2	1	11
Total	10	10	3	6	5	3	37

Table 5. *Factor VIII associated hepatitis. Hepatitis B sequelae*

Clinical category of hepatitis B	Total	Deaths	Carriers of HB_sAg	Follow up not complete	Secondary cases in family
Icteric	21	1	2	6	0
Anicteric	5	0	2	1	1
Symptomless (HB_sAg only)	4	0	1	2	1

Hepatitis B

The clinical presentation of 30 cases of hepatitis B infection are shown in Table 3. Four cases had no clinical symptoms or signs and were detected when a blood test was positive for HB_sAg. A further 7 patients at Alton and Bournemouth for whom pre- and post-infection sera were available showed evidence of symptomless infections by seroconversion with HB_s antibody and hepatitis B core antibodies (anti-HB_c). If those with and without symptoms (seroconversion and HB_sAg positives only) are compared (Table 4) it can be seen that a higher proportion of symptomless infections occurred under the age of 20 years. This is known to be a feature of hepatitis B due to causes other than blood transfusions.

The sequelae of hepatitis B infection so far as they are known are shown in Table 5. One patient died in the acute stage of his illness, and it is thought that hepatitis B partially contributed to his death. Five patients have become persistent carriers of HB_sAg for at least 1 year. One of these presented with anicteric hepatitis complicated by a persistent arthropathy. He developed persistent hepatitis which resolved after 2 years. His serum is still positive for HB_sAg. His wife subsequently developed acute hepatitis B and has fully recovered. A second patient was found

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Table 6. *Factor VIII associated hepatitis attack rates related to batches transfused*

Batch	Total patients transfused with batch	Patients receiving this product for first time with this batch	Solid phase RIA test for HB_sAg	Hepatitis		
					Hepatitis B	
				Non-B hepatitis	With symptoms	Without symptoms
P	30	30	NT	0	0	0
Q	85	55 (2 died)	NT	6 (11·3)	3 (5·6)	1
R	55	38	NT	3 (7·8)	7 (18·4)	1
S	117	74	Positive	10 (13·5)	6 (8·1)	5
T	116	66	Positive	13 (19·6)	5 (7·5)	0
U	75	37	Positive	9 (24·3)	2 (5·4)	2
V	79	33	Positive	3 (9·0)	3 (9·0)	2
W	86	21 (1 died)	Negative	3 (15·0)	0	0
X	52	17	Negative	1 (5·8)	0	0
Y	6	3	Negative	0	0	0

Figures in parentheses indicate percentages.
Patients who died excluded from calculation of attack rates.

Table 7. *Factor VIII associated hepatitis* 1974–5. *Age specific attack rates*

Age (years) ...	<5	6–10	11–20	21–30	31–40	41–50	51–60	61+	NK	Total
Non-B hepatitis	0/12	5/63	13/124	13/69	8/49	1/20	2/13	3/12	3/9	48/371
%	0	7·9	10·4	18·8	16·3	5·0	15·3	25·0	33·3	12·9
Hepatitis B	0/12	8/63	8/124	3/69	5/49	1/20	1/13	2/12	2/9	30/371
%	0	12·6	6·4	4·3	10·2	5·0	7·6	16·6	22·2	8·0

to have become a carrier of HB_sAg after a transfusion of Brand 'L' when his father contracted acute hepatitis B. The father remembered pricking his finger months before while administering Factor VIII concentrate to his son. One patient who seroconverted without symptoms now has some evidence of chronic liver disease without persistent HB_sAg in his serum. The results so far suggest that patients with mild or symptomless infections may be more prone to chronic sequelae.

Attack rates

Related to batch implicated

Table 6 shows the attack rates for B and non-B hepatitis related to different batches. Each attack rate has been related to the total number of patients who received a transfusion of Brand 'L' for the first time when they were transfused with a particular batch. Because of the high proportion of affected batches it would be likely that any patient previously transfused with Brand 'L' would be immune to hepatitis B or non-B virus(es). Non-B hepatitis had a higher attack rate than hepatitis B in all batches except 'R'. This may reflect a higher incidence of non-B hepatitis infection in the country of origin of the plasma pools from which

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the batches of Brand 'L' were made compared with the U.K., with a resultant lower prevalence of antibody to non-B hepatitis compared with anti-HB_s in British haemophiliacs. The reason for the higher attack rate for hepatitis B compared with non-B hepatitis in batch 'R' is not known.

The apparent fall in numbers of cases of hepatitis associated with batches 'V' to 'Y' compared with 'P' to 'U' may be due to one or more of the following factors: (1) Fewer patients were given Brand 'L' for the first time with batches 'V' to 'Y' compared with 'P' to 'U'. (2) A decline in the proportion of infected batches. (3) All batches of concentrate coming into use after 'V' were made from plasma donations screened for HB_sAg by RIA, whereas before this they were screened by IEOP only.

Age specific attack rates

These are shown in Table 7. The incidence of non-B hepatitis is apparently higher than that of hepatitis B in all but the 6–10 age group. This may reflect a higher ratio of subclinical to clinically apparent infection in the non-B cases, since only patients with clinical symptoms were included in the survey.

The high hepatitis B attack rate for patients over 30 years of age reflects transfusions of patients with relatively mild disease who were transfused with large pool material for the first time for some special clinical indication, e.g. an operation.

Related to severity of disease

This information is given in Table 1. Two hundred and fifty-six out of 371 patients transfused had severe disease with less than 2% Factor VIII activity. However, it is known that Factor VIII activity is not completely correlated with the severity of a patient's disease, and therefore it is likely that there were quite large variations in the amount of Factor VIII that different patients in this group received in any one year. Variation in the amount of transfused material has been shown to be correlated with variation in susceptibility to hepatitis (Craske *et al.* 1975; Kaspar & Kipnis, 1972). Nevertheless, the attack rates for patients with Factor VIII levels > 2%, including Von Willebrand's disease patients, etc., were higher for non-B hepatitis (9 cases/54 transfused, 16·6%) than those with < 2% Factor VIII (25 cases/253 transfused, 9·8%). Similarly, severe haemophiliacs with inhibitors had a high attack rate (9 cases/40 transfused, 22·5%).

The attack rates for hepatitis B were lower but were also high in patients with mild haemophilia.

Antibody studies

The availability of pre-and post-transfusion sera from most of the patients at Alton and Bournemouth enabled us to assess the association of anti-HB_s with immunity to hepatitis B. Table 8 shows that there is significant protection in patients who had HB_s antibody in serum specimens taken before they were transfused with one or more of the suspect batches of Brand 'L'.

In Table 9 the attack rates for hepatitis B infection in patients at Alton and Bournemouth who received transfusions of Brand 'L' in 1974 are compared with the rates in those who received other products. Thirteen out of 45 patients who

Table 8. *Factor VIII associated hepatitis B Alton and Bournemouth. Association of HB_s antibody with immunity to hepatitis B*

	Hepatitis B infection (includes seroconversions)	No hepatitis B infection	Total
HB_s antibody positive*	0	30	30
HB_s antibody negative†	13	1	14
Total	13	31	44

* Includes HB_s antibody positive by RIA and/or passive HA.
† Excluding carriers of HB_sAg.

Table 9. *Factor VIII associated hepatitis B. Bournemouth and Alton outbreaks*

(Attack rates – patients for whom pre-infection sera were available)

Treatment group	Evidence of infection with HBV (Total)	Evidence of infection with HBV (No. 'non-immune')
Brand 'L'	13/45 (28·8%)	13/14 (92·8%)
Other products	1/14 (7·1%)	1/8 (12·5%)

received Brand 'L' developed evidence of hepatitis B infection. None of these 13 had detectable HB_s antibody before treatment with Brand 'L'. Of the remainder, 31 did have antibody (detectable in 28 by PHA, and in 3 by RIA only). Thus the incidence of infection in the 'non-immune' was 92·8%. In comparison one out of 14 patients treated only with other products developed evidence of hepatitis B infection although 8 had no detectable antibody – an incidence of infection in the 'non-immune' of 12·5%.

Relation of clinical to subclinical infection

It was not possible to estimate this relationship for non-B hepatitis as no specific tests were available. For hepatitis B, at Alton and Bournemouth, pre-infection serum specimens were available from 44 patients. Of these 30 were anti-HB_s positive by RIA or PHA or by both. Thirteen out of 14 antibody negative patients developed Factor VIII associated hepatitis B infection. Six of these were clinically overt and 7 subclinical.

CONCLUSIONS

(1) This survey shows that the introduction of freeze-dried commercial Factor VIII prepared from large plasma pools obtained by plasmaphaeresis from paid donors for the treatment of U.K. haemophiliacs was associated with the occurrence of one or more attacks of hepatitis in 66 patients out of a total of 371 transfused (17·7%). The mainstay of treatment before 1974 was Cryoprecipitate, each bag of which was prepared from one or two plasma donations obtained from U.K. volunteer donors. This was supplemented by a limited quantity of NHS freeze-dried Factor VIII prepared from pooled plasma from volunteer donors. The reported incidence

of hepatitis (Biggs, 1974) before the introduction of commercial concentrate was about 1·8 %. However, the methods used in our study differ from the earlier work and therefore a comparison of NHS and commercial Factor VIII using the methods of this survey is now in progress.

No cases of hepatitis B were observed after transfusion of the last 3 batches of Brand 'L'. These were negative for HB_sAG by RIA whereas the first 7 batches of Brand 'L', 4 of which were positive for HB_sAg by RIA, produced a total of 26 cases out of a total of 331 patients transfused (7·8 %). Early returns for 1976 show that there is a significant number of hepatitis B cases associated with Factor VIII concentrates which are negative for HB_sAg by RIA, which indicates that RIA screening of donors does not entirely eliminate the risk of hepatitis B infection.

(2) The mortality among the transfused patients who did not develop hepatitis was 3/308 (1·0 %), whereas among patients who developed hepatitis it was 2/66 (3·0 %). One of the latter deaths was probably not related to hepatitis so that the mortality associated with Brand 'L' is probably better expressed as 1/66 (1·5 %).

(3) The incidence of chronic sequelae due to hepatitis B and non-B hepatitis in haemophiliacs is at present unknown. Five out of 30 patients who contracted hepatitis B are now carriers of HB_sAg in their serum. Since liver biopsy is unjustified in these patients the criteria by which chronic liver disease is diagnosed will need to be carefully assessed. As a preliminary step we intend to follow up patients who contracted Factor VIII associated hepatitis to assess the general health, incidence of abnormal LFTs, and the HB_sAg and antibody status of these patients.

(4) Recent evidence (Barker, Peterson, Shulman & Murray, 1973; Prince, Hashimoto, Newrath & Trepo, 1975) has shown that despite the association of anti-HB_s with immunity to hepatitis B, second attacks of transfusion associated hepatitis B can occur if the challenge dose of virus is large enough. It is also evident that secondary symptomless hepatitis B infections could give rise to a HB_sAg carrier state with chronic liver disease. It is obviously important to find out whether this occurs in practice. Current evidence from studies at Alton and elsewhere suggest that patients receiving regular transfusions of large pool material maintain sufficient immunity to resist any secondary infections, and the incidence, if it does occur, is probably low. One group who might be at risk are patients with Factor VIII inhibitors who are transfused at irregular intervals with large doses of Factor VIII and other products.

(5) We do not yet know the nature of the non-B hepatitis we have described. The epidemiology of the disease, the definite incubation periods observed, the association with commercial plasma derivatives and the absence of illness when a convalescent patient is transfused with batches producing hepatitis in other patients – suggesting the acquisition of specific immunity – are all consistent with the view that an infective agent is involved, and elicits specific immunity.

We have been unable to exclude the possibility of hepatitis A, but the evidence of other work (Feinstone *et al.* 1975; Mosely, Redeker, Feinstone & Purcell, 1977) suggests that this is unlikely. We would expect hepatitis A to be followed by secondary cases, but we failed to detect these cases of non-B hepatitis in two outbreaks and similar observations were made independently in a third (P. Jones,

personal communication). Further work may show whether more than one agent is involved as is suggested by the observations of Moseley *et al.* (1977) in drug addicts.

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