HE6.

Public Health Laboratory Service

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10th January, 1983

Our ref JC/PH Your ref

Dr. D. Walford,
Department of Health and Social Security,
Hannibal House,
Elephant and Castle,
LONDON SE1 6TE

Ackd

Dear Dr. Walford,

Enclosed is a copy of a letter we plan to submit to the Lancet which gives the current situation with regard to the risk of non-A, non-B hepatitis after first exposure to factor VIII. The reason for this is that drug companies are planning to introduce 'hepatitis reduced' products, and it seems likely that attempts may be made to use the method of doing trial transfusions on a named patient basis and not submitting them to formal clinical trial.

The problem related to the investigation of factor VIII related Acquired Immune Difficiency Syndrome (AIDS) has been satisfactorily resolved. We will report any patient detected in the U.K. who has received U.K. commercial factor VIII direct to C.D.C. and will at the same time notify C.D.S.C. at Colindale. I have obtained Dr. Galbraith's consent to this arrangement, and I intend to produce a short note in the communicable disease report describing the present situation.

Kind regards,

Yours sincerely,

GRO-C

J. Craske
Consultant Virologist

ENC:

RISK OF CONTRACTING FACTOR VIII ASSOCIATED NON-A, NON-B HEPATITIS AFTER FIRST EXPOSURE TO LARGE POOL CONCENTRATES - IMPLICATIONS FOR TRIALS OF HEPATITIS 'REDUCED' FACTOR VIII AND IX

Dr. Crawford and his colleagues (Lancet Nov. 27th, 1982 p1220) are correct when they attribute a high risk of contracting non-A, non-B hepatitis with first exposure to factor VIII concentrates. In a prospective study undertaken at the Oxford Haemophilia Centre since March 1981[1], we have assessed the risk of contracting non-A, non-B hepatitis within 6 months of a treatment episode in patients transfused with one brand of either NHS factor VIII prepared from plasma obtained from U.K. volunteer blood donors, or commercial factor VIII manufactured in the U.S.A. All patients had mild coagulation defects and were prospectively followed for 9 months after a treatment episode requiring cover with factor VIII. So far 30 patients have been studied of whom 16 (53%) contracted non-A, non-B hepatitis. No cases of hepatitis B were found. Of the 16 patients who contracted hepatitis, all but 2 received one batch of factor VIII concentrate and the remaining two patients each received material from 2 batches with their current treatment episode.

The accompanying table shows the relationship of the number of batches of factor VIII of all brands each patient had received prior to their current treatment episode to the attack rate of non-A, non-B hepatitis. Sixteen out of a total of 23 patients who had received 4 batches of factor VIII or less prior to their current treatment episode contracted non-A, non-B hepatitis (69.5%), whereas all 7 patients who had received 5 or more batches prior to their current treatment episode failed to develop hepatitis ($p = <0.01$) ($X^2 = 7.83$). Seven out of eight patients who received NHS factor VIII and had received no concentrate previously developed non-A, non-B hepatitis. Each patient received between 1,880 and 27,800 factor VIII units from one batch of factor VIII with pool sizes of between 1,413 and 2,504 plasma donations. The attack rates for NHS and US commercial factor VIII appear similar, but the number of patients so far studied is not sufficient to be certain. We have been unable to obtain accurate estimates of the pool size of US commercial factor VIII.

Recently several attempts have been made to render factor VIII and IX concentrates free of non-A, non-B hepatitis viruses by biophysical methods. These have included UV light and β-propiolactone, (2) and heat ($60^{\circ}C$ for 10 hours (3))in the presence of substances which stabilise blood clotting factors. Since there are no methods of assaying the infectivity of preparations containing non-A, non-B hepatitis viruses other than by chimpanzee inoculation

or parenteral injection in man, it is important that any new 'hepatitis reduced' factor VIII or IX concentrate should be assessed by suitable prospective trials in patients with no known previous exposure to factor VIII or IX concentrates. These products are likely to be expensive, and in our opinion it would be valueless to use these preparations in patients who have received more than 5 batches of factor VIII, as it is likely that they have already been exposed to all non-A, non-B hepatitis viruses commonly associated with transfusion hepatitis.

There is no evidence of which we are aware that indicates that re-exposure to non-A, non-B hepatitis viruses present in concentrates received by patients with severe coagulation defects predisposes them to a higher incidence of serious chronic liver disease than patients with mild disease who received less frequent transfusions. If the 'hepatitis reduced' concentrates prove to be associated with a reduced risk of non-A, non-B hepatitis with an insignificant loss of factor VIII activity, then these products should be reserved in the first instance for patients with no prior exposure to factor VIII concentrates or those who have received less than 5 batches of factor VIII in the past. Similar considerations would apply to NHS factor IX concentrate, but we have as yet no accurate information concerning the risk of non-A, non-B hepatitis associated with NHS factor IX concentrate. Another study in patients undergoing open heart surgery [4] reported an attack rate of 100% non-A, non-B hepatitis related to transfusions of factor IX concentrate, whereas an attack rate of 3% was reported in patients who received transfusions of whole blood only.

Yours sincerely,

J. Craske, C.R. Rizza, Mary Fletcher, Joan M Trowell
Oxford Haemophilia Centre
Churchill Hospital, Oxford.

REFERENCES

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2) Heinrich, D., Kotitschke, R., Berthold, H. Clinical evaluation of the hepatitis safety of a β-propiolactone/ultraviolet treated factor IX concentrate (PPSB) Thrombosis Research 1982; 28: 75-83.

3) Heimburger, N., Schwinn, H., Kumpe, G., Mauler, R., Kroeninger, A., Kehnen, B., Rothmann, P., Schimpf, K. Hepatitissicheres Faktor VIII (F.VIII) Konzentrat. Blut 1981; 42: 129.

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RELATIONSHIP OF PAST TRANSFUSION HISTORY TO ATTACK RATE OF NON-A, NON-B HEPATITIS AFTER TRANSFUSION WITH FACTOR VIII CONCENTRATE

	NUMBER OF BATCHES OF FACTOR VIII RECEIVED PRIOR TO CURRENT TREATMENT												
	0	1	2	3	4	5	6	7	8	9	10	>10	TOTAL
Number of patients who developed hepatitis after factor VIII	9	3	1	2	1	0	0	0	0	0	0	0	16
Number of patients not developing hepatitis after factor VIII	1	1	2	1	2	1	1	0	2	0	1	2	14
ATTACK RATE	9/10	3/4		4/9					0/7				16/30
PER CENT	90	75		44.5					0				53.3