

SURVEILLANCE FOR EVIDENCE OF NANBH TRANSMISSION
BY BPL CONCENTRATES 8Y AND 9A, DRY HEATED 80° 72H.

An analysis of selected data, collected in 1985-1987 by:

Dr. B.T. Colvin and colleagues; patients 101, 103, 104, 105, 106, 107,
108, 109, 206.
Dr. C.R. Rizza: patients 001, 002, 003, 004, 201, 202, 209.
Dr. F.G.H. Hill: patients 006, 110.
Dr. P.B.A. Kernoff: patients 102, 203.
Dr. H.M. Daly and Dr. P.C. Taylor: patient 005.
Dr. P.C. Taylor: patient 111.
Dr. C.R. Rizza and Dr. R.T. Wensley: patient 112.
Dr. M.W. Kenny: patient 007.
Dr. V.E. Mitchell: patient 204.
Dr. D.N. Whitmore: patient 205.
Dr. C.J.T. Bateman: patient 207.
Dr. P. Bolton-Maggs: patient 208.
Dr. H.M. Daly: patient 210.

Report assembled by Dr. J.K. Smith, Plasma Fractionation Laboratory,
Oxford, for Blood Products Laboratory, Elstree.
16th September, 1987.

Surveillance for evidence of NANBH transmission by BPL concentrates
8Y and 9A, dry heated 80° 72h

This updated analysis, covering approximately two years of study in several Haemophilia Centres, is stricter than the one presented to HCDs last year, in terms of admission criteria and assessment of compliance. Since some will still find these standards too lax, sufficient detail is given to allow further categories of patient to be excluded. There is a limit to the number of possible permutations that can be handled in a brief report, but I will be pleased to analyse the primary data in any way requested by a Director who has submitted patient data.

Admission criteria

This analysis is restricted to three classes of patient:

Series 001 et seq.	7 patients receiving 8Y; no previous exposure to any blood product.
Series 101 et seq.	12 patients receiving 8Y; previously exposed only to single donor products.
Series 201 et seq.	10 patients receiving 9A; no previous exposure to any blood product.

The view that exposure even to single donor products may confer immunity to NANBH will be acknowledged in a new phase of these trials. Meanwhile it may be admitted that the risk of coming to erroneous conclusions in the present analysis is statistical, determined by the incidence of NANBH in the donor population in the UK and the number of units to which the patient was exposed - fewer than 100 in every case.

There is a view that patients who have not been exposed to recent or frequent infusions of blood products may remain highly susceptible to NANBH, and that LFT surveillance in these patients following 8Y or 9A may be of substantial value. However, such patients will not be considered in this analysis.

The liver enzyme status of each patient is included in Table 1, since there is some contention about the definition of "normal LFT at entry".

No patient undergoing a second or overlapping course of treatment with a further batch of product has been included in this analysis, even when defined as "adequately followed" after exposure to the first batch.

Definition of "adequate follow-up"

This study was started before "ISTH criteria" - not yet published or subjected to critical discussion in a refereed publication - were widely adopted in this field. With very few exceptions, the degree of latitude in sampling dates is not specified in comparable published trials. This analysis defines as "adequate follow-up":

- (1) No fewer than three tests in the first three months (defined as days 7-91 after first infusion, allowing seven days' latitude on a 2-12 week period). An average of 5.8 tests was achieved in the group analysed.
- (2) No fewer than four tests in the first four months (defined as days 7-119 since first infusion, allowing seven days' latitude on a 2-16 week period). An average of 6.8 tests was achieved in the group analysed.

Patients with fewer tests are held by some to offer valuable statistical information but they will be discussed in this analysis only where a "suspicious event" has occurred.

Apart from a few cases with unexplained late rises in LFTs, most published data indicate that NANBH should be detected in the first 2-12

weeks after infusion.

Although published cases show that virtually all significant LFT rises would be picked up by testing at 4, 8 and 12 weeks (in some publications the intervals are given only approximately), ISTH criteria require testing at fortnightly intervals to 16 weeks; latitude around this 14 day interval is not specified. The present analysis allows readers to drop patients from consideration if the maximum gap between tests is thought to be excessive in any case:

Cases with a gap >28d in the period 7-91d: 002, 003, 102, 110, 205, 206, 207.

Cases with a gap >35d in the period 7-91d: 002, 003, 102.

Cases with a gap >28d in the period 7-119d: 001, 002, 003, 005, 006, 102, 110, 201, 204, 205, 206, 207.

Cases with a gap >35d in the period 7-119d: 002, 003, 005, 006, 102.

Results in eligible patients "adequately followed" for 16 weeks

None of these patients had an AST or ALT level >2.5 x the upper limit of locally defined normal, confirmed by a prompt repeat test, within the prescribed period.

Two events deserve comment. Patient 206 showed a spike of ALT to 102 iu/ml on day 34, but was normal on day 6 and day 55, the nearest dates on which he could be tested. Patient 101 had a spike of ALT to 107 iu/ml (>2.5 local normal level) on day 133, after the 16 week surveillance period analysed here. The rise was not confirmed five days later; AST and other LFTs were normal throughout.

If these data are tentatively accepted as indicating zero incidence of NANBH transmission among these 29 patients, the best that can be said is that the true incidence (95% confidence limits) is in the range 0-10%.

Batches exposed

It is equally important to realise the breadth of exposure of this adequately-followed group of patients. These 29 patients received a total of 28 batches at or within two weeks of first exposure. The number of donors represented in these batches was approximately 180,000. Approximately 0.1% (possibly as high as 0.3% in some areas) of UK donors are thought to be able to transmit NANBH by whole blood or component transfusion.

These batches were used at random from BPL's routine manufacturing process, or nominated only for the purpose of giving as many batches as possible to more than one patient.

Possibly relevant data from ineligible patients

Additional data, too heterogeneous for this summary analysis, have been collected on infrequently treated patients; patients, mainly children, maintained on 8Y because they were HIV sero-negative although exposed to (mainly NHS) products likely to have transmitted NANBH; and patients who could not be adequately followed for a variety of reasons - most commonly, reluctance to subject infants to fortnightly venepuncture.

Among 25 such patients having at least one LFT in the first four months, three "suspicious events" have been noted.

Patient P showed a spike of AST >2.5 x upper limit of normal on day 78, but a normal level on days 66 and 81.

Patient S showed a spike of AST >2.5 x upper limit of normal on day 190, long after formal surveillance had ended. The last sample on day 102 had been negative. The ALT on day 190 was normal.

Patient M, inadequately followed on his first two batches of 8Y, showed a

significant rise of ALT and AST nine weeks after starting a third batch, confirmed at 11 weeks. Although this patient had had an undetermined amount of single donor cryoprecipitate before 8Y, it is said that no other type of concentrate was administered during the relevant period. The implicated batch had not been nominated for trial and there is no supporting evidence from any other eligible patient in compliance.

Conclusion

It is not possible to determine the true incidence of transmission of NANBH by 8Y and 9A from this imperfect evidence, but the apparent near-zero incidence justifies the inclusion of a further series of patients in a more formally controlled prospective trial, to be co-ordinated by Dr. Rizza and Dr. Kernoff.

Table 1. Surveillance from 1-13 weeks and 1-17 weeks

PATIENT CODE	CONC.	BATCHES EXPOSED	AGE YEARS	PREVIOUS EXPOSURE	ENZYME ALT/AST	iu/ml		NO. OF TESTS	
						PRE	MAX	d7-91	d7-119
001	8Y	1	37	None	AST	8	17	5	5
002	8Y	1	35	None	AST	18	24	4	5
003	8Y	1	27	None	AST	14	32	4	5
004	8Y	1	30	None	AST	12	32	7	8
005	8Y	1	11	None	AST	39	48	5	6
006	8Y	1	1	None	ALT	45	55	3	4
007	8Y	1	30	None	AST	37	47	7	8
101	8Y	2	5	Cryo	ALT	20	35*	7	11
102	8Y	1	32	Cryo in 1977	AST	16	39	3	4
103	8Y	1	16	Cryo in 1980	ALT/AST	24/66	30/56	8	9
104	8Y	3	44	Cryo in 1976	ALT/AST	5/20	12/20	8	8
105	8Y	1	18	Cryo in 1982	AST	35	30	8	9
106	8Y	3		Cryo in 1976/7	ALT/AST	13/23	16/30	7	8
107	8Y	1	85	Plasma 1961	ALT/AST	24/32	38/66	6	8
108	8Y	1		Cryo	AST	-	39	6	7
109	8Y	2	17	Cryo in 1984	AST	13	20	6	7
110	8Y	1	10	Cryo in 1986	ALT	17	16	3	4
111	8Y	1		Cryo in 1984	AST	31	33	6	7
112	8Y	1	47	Cryo in 1974	ALT/AST	-/11	35/-	6	7
201	9A	1		None	AST	30	38	7	8
202	9A	1	69	None	AST	15	20	5	6
203	9A	1	<1 mo	None	AST	23	52	5	7
204	9A	1	17	None	ALT	20	24	9	10
205	9A	1	13	None	ALT	-	18	5	6
206	9A	1	5	None	ALT/AST	32/55	102/65*	3	4
207	9A	1	22	None	AST	20	31	5	6
208	9A	1	53	None	ALT	19	40	6	7
209	9A	1		None	AST	19	44	5	6
210	9A	4	10	None	ALT	11	21	6	7

*But see "Results" for comment.