Joint IABS/CSL Symposium on Standardization in Blood Fractionation including Coagulation Factors
Melbourne, Australia, 1986
Develop. biol. Standard., Vol. 67, pp. 323-325 (S. Karger, Basel, 1987)

Plasma Fractionation Laboratory,
Churchill Hospital, Oxford, 0X3 7LJ, U.K.

INTERIM RESULTS OF SURVEILLANCE FOR NANBH IN PATIENTS RECEIVING HEATED CONCENTRATES PRODUCED IN ENGLAND

J.K. Smith, Lowell Winkelman and P.A. Feldman

ABSTRACT

Coagulation factor concentrates prepared in England are all subjected to heating in solution or in the lyophilised state. Concentrates of factor VIII, factor IX (II and X), factor VII and factor XI are terminally heated in the lyophilised state at 80°C for 72 h but the current fibrinogen concentrate withstands only 70°C for 24 h.

33 patients receiving factor VIII concentrate (code 8Y) and factor IX concentrate (code 9A) for the first time have had regular liver function tests (LFTs) and we have at least some data on 26 of them exposed for > 3 months. Of these 26 patients, four had received no blood products before 8Y, 15 had received only cryoprecipitate before 8Y, and seven had received no blood products before 9A. Nine have missed only one or none of their two-weekly tests, four have missed two or three tests and on the remaining 13, the LFT follow-up has been unsatisfactory, although in some cases clinical examination has been helpful. 12 batches of 8Y from > 70,000 donations and seven batches of 9A from > 40,000 donations have been used. In 13 patients who have had regular prospective LFTs, none has had an ALT or AST level above twice normal. One patient followed only irregularly has shown an isolated ALT rise at eight weeks, unconfirmed at nine or at 17 weeks.

INTRODUCTION

The range of heated concentrates available in England and Wales in 1986 is shown in Table I. AT III has been in use for nearly three years in 20 patients. 11 of these patients, previously untreated with large-pool concentrates, and using 17 batches of AT III, have been subjected to surveillance for NANBH, with no

Table I. Concentrates available in England and Wales, 1986

Heated in solution, 60°C for 10 h	
Albumin	(+ caprylate)
AT III	(+ citrate)
Factor XIII	(+ sorbitol)
Heated after lyophilisation in final container	
Factor VIII (8Y)	80°C, 72 h
Factor IX (II and X) (9A)	80°C, 72 h
Factor VII	80°C, 72 h
Factor XI	80°C, 72 h
Fibrinogen	70°C, 24 h

suspicious events. Three previously untreated patients on two batches of pasteurized factor XIII concentrate have been the subject of monthly surveillance: one of these patients has shown two isolated transaminase elevations, not meeting current criteria for suspicion of NANBH.

Factor VIII concentrate (product code 8Y) is a new concentrate introduced just a year ago, prepared by precipitation of fibrinogen and fibronectin with heparin, reprecipitation of the supernatant factor VIII by glycine and sodium chloride, desalting, freeze-drying and severe heating of the finished concentrate in its final vial. The factor IX concentrate 9A is a very long-established DEAE-cellulose eluate containing factors IX, II and X, now protected by the addition of a low concentration of AT III before drying, and severely heated in the final vial.

Since these concentrates receive the same regime of dry heating (80°C for 3 days), and since experience of NANBH surveillance has been the same, they will be considered together for discussion of NANBH transmission. Our ideas on criteria for patient selection and follow-up have changed somewhat with experience, and the interim data do not meet everyone's definition of a well designed prospective clinical trial, so we use the term «surveillance» rather than trial.

On other occasions, evidence will be presented about the susceptibility to NANBH transmission of patients who have received large-pool concentrates only infrequently in the past, but data are given here about patients in only three categories, shown in Table II.

Table II. Three categories of patients reported here

- 4 patients who had no blood products before 8Y.
- 15 patients who had only cryoprecipitate before 8Y.
- 7 patients who had no blood products before 9A.

The intended surveillance schedule for these groups, incorporating broadly the recent ISTH recommendations for hepatitis trials, have as their crucial element two-weekly transaminase measurements for the first three months. Only one published case seems to have had a longer incubation period than three months.

Although the abstract written earlier refers only to numbers of patients, we have included in these updated summaries a number of patients who have had second or third batches of concentrate, and we will count each sequence as a distinct «exposure».

RESULTS

Of 35 «exposures», 13 follow-ups have missed only one or none of the fortnightly liver function tests (LFTs); four have missed two or three tests; and 18 have been unsatisfactory. Twelve batches of factor VIII have been used from a total of > 70,000 donations, and seven batches of factor IX from > 40,000 donations.

In all these patients who have had regular prospective LFTs, none has had a transaminase level above twice normal.

One patient followed only very irregularly and therefore not originally entered in the trial has shown a single isolated ALT rise at eight weeks, which was *not* confirmed at nine or at 17 weeks. Two other patients receiving the same batch have been quite well.

DISCUSSION

We do not apologise for presenting cases with less than immaculate follow-up, for two main reasons. Firstly, many of the patients who missed an LFT test, for one reason or another, were seen at the clinic at the correct time and thought most unlikely on subjective clinical grounds to have had hepatitis since the last visit. Secondly, we have tested many of our imperfect follow-up patterns against the patterns of elevated transaminases in three published studies (1-3). We have concluded that very few of the published cases of NANBH transmission would have been missed by the actual pattern of testing of most of our 17 best cases. It should be noted that one or two of the published cases might have been missed even by strictly following the ISTH recommendations on frequency of testing.

Let me again concede that this collection of data of variable quality does not carry the full authority of a formal prospective clinical trial. However, when all reservations have been made about imperfect follow-up data, the weight of this varied evidence justifies our asking clinicians to put many more previously untreated patients into a more formal trial, using even more batches of product.

Although these are only interim results on a limited number of batches, we think we are justified in thinking that the severe heating has been more effective in preventing transmission of NANBH than the milder heating accorded to the Hyland (1) and Armour (3) products in studies published last year: It is too early to know whether NANBH transmission has been eliminated by severe dry heating, or whether we may see transmission by only a few batches, as has occurred with Alpha's factor VIII concentrate heated in heptane (2).

ACKNOWLEDGEMENTS

This paper is a collection of information supplied mainly by the following Directors of Haemophilia Centres in England, whose contributions are gratefully acknowledged: Dr. Rizza, Dr. Colvin, Dr. Kernoff, Dr. Hill, Dr. Daly, Dr. Bateman, Dr. Mitchell, Dr. Whitmore, Dr. Baugh, Dr. Sheppard, Dr. Shirley.

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