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Notes of the Haemophilia Reference Centre Directors Meeting, Blood Products Laboratory, Elstree 10/12/84

Present:

Prof. A Bloom (Chairman)
Dr R S Lane (BPL)
Dr T Snape (BPL)
Dr M J Harvey (BPL)
Mr P Prince (BPL)
Mr N Pettet (BPL)
Dr J K Smith (BPL)
Dr P Kernoff
Dr P Jones
Dr C Ludlam
Dr F Preston
Dr E Mayne
Dr H Gunson
Dr A Smithies (DHSS)
Dr J Cash
Dr I Delamore
Dr P Mortimer (PHLS)
Dr J Craske
Dr C Forbes
Dr C Rizza
Dr G Savage
Dr R Tedder (Middx Hosp.)
Dr I Temperlay

Agenda

In addition to the previously circulated agenda, an aide-memoir was tabled by the Chairman. This covered several points for discussion at the meeting.

Item 1 Introduction to the meeting

The Chairman outlined that the resulting publicity surrounding the events in Newcastle and Australia, and the continuing work on HTLV III, has precipitated todays meeting.

Item 2 (i) HTLV III antibody screening

Dr Tedder reviewed the current situation by saying that the Gallo cell line was available for investigation although the USA had made the isolates difficult to obtain. The British isolate required an organisation to handle the bulk virus culture: Porton (PHLS) and Wellcome are the only ones

so far interested. There are problems in obtaining the antigen. Dr Tedder's test uses a cruder antigen.

Several problems remained in getting the test into the NBTS:

1) cost of the kit ?
2) the extra staff required to run the tests ?
3) advice to donors found to be HTLV lll positive ?
4) how soon can the test be introduced ?

It was noted that G.U.M. clinics are resistant to screening because of the social problems created.

Dr Mortimer stated that the PHLS was under pressure to be involved with introducing a 'kit' for availability throughout the PHLS.

In summary, testing was likely to be recommended for patients and contacts in addition to the 2500 Haemophiliacs who would require regular testing, (the testing of contacts for Haemophilia alone would be of the order of 10,000).

If one broadened the test to take in the NBTS, it was clear that many thousands of tests would be required each year.

(ii) Availability of tests

Dr Craske advised that currently, the reagents were only available on a research basis, and that substantial resources would be required to enable the proposed workload to be undertaken.

It was considered that to know the antibody status of every haemophiliac would be advantageous in determining the regime for treatment. However, the limited resources made it impossible to do routine tests at the moment.

Some discussion took place on which organisation would be best placed to organise the testing, and whether DHSS financial support would be forthcoming. Dr Lane (BPL) suggested that if resources were available BPL would play a part coordinating the endeavour. Dr Smithies advised that she would take all these points back, to the DHSS for consideration.

The Chairman, in summary, advised the meeting that he would write to Dr Smithies after the meeting delineating precisely the problems.

(iii) Blood donor testing

It was suggested that the testing of donors requires either 1) mass commercialisation of a British test or 2) application of a current commercial test. Confirmed that testing would be introduced at two centres early in 1985 prior to widening availability to the rest of the NBTS.

Dr Gunson advised that it would be preferable to test all donors. However if resources were limited it might be better to concentrate testing at the major 'risk' centres.

Dr Cash was concerned that no central organising body was being contemplated for the test programme. This view was confirmed by Dr Tedder who was concerned that the pace of test advancement was so fast that the scientists were left to introduce a test as soon as possible. There was also considerable concern expressed over the lack of financial support from the DHSS.

(iv) Significance of HTLV lll antibody tests

Dr Tedder outlined the significance of HTLV lll from a virologist viewpoint.

a) the presence of antibody may be a suggestion of developing AIDS, but not necessarily so.
b) there could well be advantages in being able to remove the antibody positive donors from the donor pool.
c) It is likely that to be HTLV lll antibody positive suggests previous exposure to the antigen. Virus can be isolated from many antibody positive persons so that one must assume that many of them are infective. In haemophiliacs the presence of antibody is probably the result of infection rather than passive transfer in concentrates. There may be a period of viraemia preceding seroconversion.

It was also noticed that some patients do not produce antibody. Thus an infected batch of concentrate would not always result in the detection of antibody in patients who had received the batch.

Dr Ludlam confirmed that in Scotland, some patients who were previously antibody +ve are now -ve. Does this suggest passive transfer of antibody ?

In summary, the Chairman outlined that HTLV lll +ve persons should be considered a risk but that one still could not assume that -ve contacts are not infective. Haemophiliacs who are positive should therefore be considered a high risk until the situation becomes clearer.

Some discussions took place on how relevant the HTLV lll antibody test was in the scientific context. It was concluded that from a social and practical view it must be considered relevant.

(v) Advice to patients and donors

Dr Jones tabled the current Newcastle policy and made observations on the contents.

With regard to the treatment of Haemophiliacs there is no change in therapy except for the holding back of prophylaxis of children by home-treatment.

All concentrate is now heat-treated commercial; advice was sought on the use of non-HT Factor Vlll and Factor lX.

Dr Jones added that in Newcastle there are three cases of organ donation by Haemophiliacs. The patients are now under surveillance. He also commented that all of his 21 staff had been tested and found -ve for HTLV lll antibody.

A long discussion took place on whether persons found to be +ve were to be informed. Several differing views were expressed. It was agreed that each clinician would decide for each case depending on the facts of the case but in general to provide information if asked for.

Item 3 (i) Factor Vlll Concentrates

It was agreed that HT product should be given to all patients, if freely available, to include those found to be antibody +ve. In the case of antibody -ve patients, it was agreed that from now on, treatment must be with HT material.

Dr Savage commented that this has and would continue to create severe financial problems for treatment centres.

Dr Tedder asked that advice to patients should go hand in hand with treatment, and outlined the recent case in the USA of a child contracting AIDS from the wife of a haemophiliac. Thus sexual counselling was also an important aspect.

It was agreed that haemophiliacs should all be given the same advice with selective advice being given based on the results of HTLV lll testing.

Dr Kernoff commented that as some 70% of haemophiliacs are now +ve it may be considered irrelevant if one tells or dosen't tell the results of testing.

The Chairman summarised by saying that testing should be instituted as soon as possible, and that information on the test results, should not be given automatically but if asked for. HT material should be given preferentially in those cases where concentrate is required. The financial consideration must be considered secondarily to the primary aim of treatment.

(It was noted that recent unpublished data from Manucci supported the effectiveness of heat-treatment. Of 21 patients given Hamophil HT, none had yet seroconverted).

Some discussion took place on the use of Factor lX. It was felt that the main problem was in balancing the risk of HTLV lll against the risk of increased thrombogenicity associated with HT - Factor lX.

(ii) Advice and testing of Staff

Dr Jones following his own experience felt it was important to show the low (or zero) risk to staff. This was supported by Dr Ludlam who considered it would be a good morale boost.

Dr Kernoff advised that any such course of action would need to pass through an ethical committee.

The meeting agreed that they would issue no advice on general testing of staff but that it should be considered in specific circumstances for large Haemophilia Centres.

Dr Tedder referred to the first known case of needle-stick in the UK, to be reported in the Lancet 15/12/84, and suggested that each Centre should carry out a safety audit with special reference to avoidance of needle-stick and simular incidents. He also remarked that Biotest Anti-HBs/Anti-CMV Immunoglobulin were reported to contain high levels of anti-HTLV III. None of the patients given this material had seroconverted so far.

(iii) Availability and use of HT Factor VIII

The Chairman outlined the choices available for haemophilia treatment. There were differing opinions on the 'risk' and/or use of NHS non HT concentrate. Some Directors felt that this material should not be used in the current circumstances, although much would depend on financial resources and the progress with NHS HT - concentrate.

Much discussion took place on the legislative aspects of the use of HT concentrate. It was unlikely, that legislation would be recommended to prevent the use of non-HT material.

In some circumstances, the alternative to not using non HT material would be no treatment.

Dr Lane stated that there could be a case for legislation on the type and length of heat-treatment required. He advised that one needed to be realistic ie one can't accept that an HT label implied a safe product. Commerical companies were being asked to reapply for licences for HT product.

Dr Mortimer reviewed the situation in that the majority of recipients are or will be sero +ve in the next few months. The use of HT material may not be required in these majority cases, although he accepted that there were other benefits (moral, social family, staff etc). If further exposure to potential virus caused more problems, then one could justify clearly the use of HT materials even if there were financial problems.

Dr Savage suggested that a task group be set up to look specifically at the AIDS problem in relation to Haemophilia. The Chairman agreed that the Reference Centre Directors would consider this.

Dr Cash urged that the financial consideration be looked at seriously. The implications for the cost of treatment to Haemophilia were enormous for the small number of patients involved.

Dr Lane added that the cost considerations spread to the NBTS, which was not just concerned with Haemophilia management. Here the cost of screening donors would be added to by BPL who would wish to test independently the plasma received at BPL.

Further discussion took place on the current price increase with HT concentrates and the likely future cost of this material. It was pointed out that because of the current media interest, patients were not treating themselves as they should.

In summary, the Chairman said that one has to accept, for the present, that it is difficult to avoid the argument that non-HT constitutes a risk. There were problems in adopting a two-tier system of treatment.

Meeting adjourned for lunch

Afternoon session

Item 3 (iv) Progress with heat-treatment of NHS Factor VIII

The Chairman began this session by outlining the current commerical supply of HT Factor VIII. Cutter, Armour, and Travenol were dry heat preparations, whereas Alpha (at 14p/iu) was wet. Hoechst also were supplying a preparation.

Dr Lane stated that BPL had begun 1984 with two objectives:-

1) a product with inactivation of non A/non B
2) a product acceptable for general use, with non transmittance of virus

R & D had been making good progress on these points which now coincided well with the current AIDS problem.

Dr Smith (BPL) then reviewed the current work programme. He added that there had been difficulties with the effectiveness of dry heat for the inactivation of non A/non B and therefore this had not been progressed as the first option. The current product had been dry-heated at 60^0C in conditions suitable for recovery of Factor VIII activity. This material had been available since March 1984 on a limited basis in solution.

The alternatives to dry heat, ie heat in solution or virus inactivation by detergent offered additional prospects for a safer product.

Dr Smith stated that the priority had been given to Factor VIII, although Factor IX was capable of being heat treated. However the problem of potential thrombogenicity was causefor concern and no HT-Factor IX would be issued even for clinical trial before animal experiments had confirmed safety.

The present stock of Factor VIII is being considered for heat treatment. Not all batches were suitable and these would remain available as non HT product.

Current work is directed to making available limited supplies of a heat treated product to April 1985, when it is expected that all batches will be heat-treated. A new product of higher Specific Activity is already being prepared which will withstand more severe heat-treatments and other treatments designed to inactivate hepatitis viruses as well as HTLV III.

Dr Lane remarked that in order to determine the effectiveness of the heat-treatment, spiking of Factor VIII with antigen was required prior to heating. The present methods used by the NHS and commercial companies may still leave an active antigen. BPL would therefore be looking for follow-up studies during 1985 with Haemophilia Centre support.

Dr Lane advised that HT material in large quantities could not be available before April as equipment had to be ordered. These had now been placed for all the required plant.

The Chairman commented that "CDC type evidence" for BPL HT batches was important. BPL would need to obtain this evidence in support of their marketing of the product. It was accepted that with limited trial facilities available, the NHS producers were in competition with commercials for trial studies.

Dr Lane advised that it was too soon to be precise on the yield losses involved, with heat treatment. Users should not assume that the higher purity product meant a higher loss yield. Observed losses so far for the standard heat-treated product were similar to those found by commercials.

Dr Craske in response to Dr Lane, advised that it was too soon to know whether the Aids implicated batch of NHS Factor VIII had caused seroconversion.

It was agreed that on general evidence, the BPL HT product would be accepted for use. Normal recovery and half-life were seen with the HT trials done so far. It was also noted that through the loss of activity, BPL would by necessity reduce the annual output of Factor V111 from the present 30 Miu level (expected loss of 15-20%).

The meeting also discussed the need to control the licensing arrangements for the use of unlicensed product. It was seen that current rules allowed companies to exploit the named patient system eg FEIBA. It was also suggested that the regulatory bodies would need to consider applications for variation orders and to determine whether the products are new formulations requiring new license applications.

Paradoxically, if variation orders for HT products were approved, this would revoke the previous licensed application and therefore non - HT product could not be used for HTLV 111 positive patients !

Dr Savage raised the problem of treatment for haemophiliacs who had only received NHS product. Until NHS HT material was available, the alternatives were commercial HT or non - HT NHS material.

Opinions varied as to whether non HT NHS product would be used. The Chairman suggested that it be left to individual treatment centres to determine their policy.

Dr Lane advised that under the circumstances, BPL would not issue non - HT product in December, unless these were required for use and a specific request was made. Non used vials should not be returned to BPL as the BPL policy was not to reissue vials previously sent to users, in line with regulatory requirements. Any vials returned would probably be destroyed or put to research use. Some HT material will be available for clinical trail purposes, but the bulk will not be available until April:- three ovens are required, one is already in use, and two are expected in March.

It was agreed that priority for NHS HT material would be given to children and past users of NHS material.

Dr Jones commented that to continue to use non HT material would be against guidelines issued by the U.S.A. groups.

Dr Cash agreed but accepted that in the UK a phasing in period was bound to occur. There were risks other than HTLV lll with commerical concentrates.

The Chairman advised that he would issue guidelines following the meeting. In summary, the first choice would be HT material followed by the judgement of the individual clinican. He also suggested that peripheral treatment centres return all non HT commercial material to the Reference Centres for transfer back to the Company involved. Most companies had undertaken in writing to accept back non HT material.

Item 4 Follow-up of patients receiving HT Factor Vlll

It was seen to be important to follow-up all patients for any evidence of seroconversion.

Dr Craske was nominated to coordinate this with the help of a small task group. Dr Lane requested that BPL HT product be included in this study. Dr's Tedder and Savage agreed to help with the preparation of a protocol, along with Dr Craske.

Dr Mortimer suggested an intensive follow-up study for at least 3 months at 2 week/1 month/ and 3 months. Until variation orders were obtained these studies would be on a named patient basis.

A rethink might be necessary if an HT product was implicated in a seroconversion. In that case, all patients receiving the batch would be carefully monitored.

On the question of finance, Dr Savage suggested that a case be put to the DHSS for financial support by representatives of the Haemophilia Directors Organisation. Any recommendations for treatment would need to be supported by recommendations for financial support. The Chairman advised that the case for more money had already been put to the DHSS.

Item 5 (i) Handling of HTLV lll positive samples

The Chairman began by outlining problems encountered in Cardiff in obtaining pathology work, as no Category lll containment laboratory was available in Wales. The recommendations in the draft document on the handling of viruses such as HTLV lll were discussed. Several members were concerned as to its content and the practical implications likely to result from its introduction.

Dr Tedder voiced his concern over the report but suggested that it was time to introduce a safety audit and a level of laboratory practice sufficient to cope with the handling of future HTLV lll problems, and sufficient to allay staff fears. He commented that past experience had shown test laboratories not to be areas of greatest risk.

The meeting was concerned on the social attitudes being adopted towards AIDS patients and Haemophiliacs. The situation was becoming very emotive, and commonsense was giving way to panic amongst donors, patients and contact groups. The Chairman advised that commonsense should prevail, and would write to David Tyrrel of the DPC expressing the members views.

(ii) Risk to Staff etc

Members agreed that the evidence so far showed little or no risk to staff treating patients. It was accepted that dental care constituted a higher risk and that steps should be taken to minimise the risk. The evidence from Hepatitis suggests that there is no aerosol risk, but that there is a risk from innoculation.

Dr Gunson advised that sexual contacts of risk donors were being discouraged from donating blood. This included haemophiliac family members.

Item 6 Advisory Statements

The Chairman stated that recommendations would be issued on the days proceedings and these would be widely circulated.

At this point Dr Lane suggested that for the remainder of the meeting, the Haemophilia Directors be allowed to have a private meeting with only themselves present. This was accepted.

The Chairman thanked Dr Lane and his staff for their presence at the meeting, and the hospitality afforded to the Directors by BPL.

N Pettet/KF/3.1.85