PROSPECTIVE STUDY OF PREVENTIVE TREATMENT IN HAEMOPHILIA

It has been suggested that the frequency of occurrence of haemarthroses in severely affected haemophiliacs can be reduced by the routine administration of factor VIII concentrates at intervals of 2 - 4 weeks (1). Prophylaxis, if effective, would reduce the frequency of bleeding episodes. No controlled trial has, as yet, been carried out to determine whether this aim can be achieved.

To benefit the patient, the frequency of spontaneous haemorrhage, traditionally treated, should approach the frequency of prophylactic administration of factor VIII. It is proposed that only clinically severely affected patients should be the subjects of trial.

The effects of prophylactic administration of factor VIII concentrates may be complex. For example, a patient may gain sufficient assurance from such treatment as to ignore symptoms which would ordinarily cause him to consult his physician. Conversely, he may be prompted to exert himself more strenuously than he might otherwise, and thereby provoke a bleeding episode. The effects of psychological influences on bleeding in haemophilia have been stressed (2). It is desirable to control these sources of potential bias by designing a trial with two specific requirements. First, the variation among patients is controlled by a 'cross-over' design, whereby each patient serves as his own comparison. Secondly, the individual variation of a single patient between high and low dose factor VIII concentrate is controlled by employment of the double-blind method. It is calculated that if prophylactic administration of factor VIII reduces the number of bleeds by 50%, then 10 patients should provide evidence for a statistically significant result.

An ideal location for carrying out a clinical trial to evaluate prophylaxis, would be a Centre where a relatively large number of severely affected haemophiliacs are closely observed daily; where the 'baseline' bleeding habits of the patients are known; and where personnel and facilities exist for separating clinical management from trial administration. Such a location is the Lord Mayor Treloar College.

I. Eligibility Criteria

All classical haemophiliacs who fulfil the following eligibility criteria will be admitted to the trial:-

1. Age - 7 years or over
2. Sex - male
3. Factor VIII level - 1% or less
4. The average number of bleeding episodes* (including haemarthroses, haematomata, epistaxes and haematuria) during the two school terms prior to admission to the trial, must exceed 7 per 100 days
5. Patients with factor VIII inhibitors will be excluded.
6. Patients in whom elective surgery is anticipated during the trial period, will be excluded or their admission to the trial delayed.
7. Patients participating in school studies with conflicting requirements, will be excluded.
8. All patients must give their informed consent as defined below, prior to the final determination of eligibility.
9. All patients should be available for study for a minimum of 4 terms.

II. Baseline Clinical Information Required

Historical information and physical findings, as detailed in the data forms, will be recorded before determination of patient eligibility.

III. Baseline Laboratory Studies Required

1. Two-stage factor VIII assay (3)
2. Factor VIII inhibitor screen (4)

IV. Trial Design

The trial for an individual patient will consist of four school terms. During two of these terms, the patient will receive once-weekly infusions of freeze-dried, Australia antigen-screened factor VIII concentrate, in a dose calculated to keep the factor VIII level above 5% for 24 hours. During the other two terms, the patient will receive an infusion of no more than 20 units of factor VIII concentrate, dissolved in a heat-inactivated sterile 1% albumen solution.

The pattern of assignment to high and low dose therapy will be by random allocation, after preliminary stratification, according to severity. Whenever possible, the trial will be completed for an individual patient within four consecutive school terms. It may be necessary under special circumstances, to delay a treatment period for an interval not to exceed one school term. The total trial period shall, in no instance, exceed six school terms.

---

* Any discrete episode of joint, muscle, subcutaneous, genitourinary or nasal haemorrhage, whether or not preceded by trauma, which in the opinion of the investigator was sufficiently well documented and serious enough to have been treated with factor VIII-containing material, regardless of whether it was, in fact, treated.

V. Division of Responsibility

To implement the double-blind requirement, it will be necessary to divide responsibility for clinical management and trial administration among several individuals, as follows:-

1. The doctors responsible for clinical management will be 'blind' to the treatment assignment. They will determine patient eligibility, complete data forms and decide treatment for bleeding episodes, when they occur.

2. The doctor responsible for trial administration will receive data forms indicating eligibility of patients for the trial. He will assign patients to a treatment schedule by reference to a table (supplied by Professor Alderson), and inform the doctors responsible for therapeutic infusions, each term, which patients are to receive high dose - and which, low dose.

3. The doctors responsible for therapeutic infusions, will administer high or low dose concentrate to patients. They will give the infusions once weekly.

   They will also give therapeutic infusions of factor VIII concentrate when required for a bleeding episode, but since they are not 'blind' to the treatment assignment, they must receive instructions about this from the doctors responsible for clinical management.

   The practical arrangements are defined in Appendix A.

VI. Informed Consent

After tentative determination of a patient's eligibility, the trial will be explained fully to the patient and the patient's parents or guardian. It is hoped that the Directors of Haemophilia Units in the boys' home areas, will assist the Trolcar Centre staff in obtaining consent for inclusion in the trial. The following points will be made clear:-

1. During the entire trial, each patient will receive an infusion once weekly of either high or low dose factor VIII concentrate.

2. The patient will NOT be told to which treatment he is assigned.

3. It must be understood that the only safe assumption for the patient to make, is that he is assigned to the low dose group. He should act accordingly by not taking undue risks, and as usual, by promptly reporting symptoms suggesting haemorrhage.

4. All patients will receive the customary treatment, such as they have had in the past, for bleeding episodes when they occur.

5. Patients must agree an intention to participate in the trial for a full four terms.

VII. Determination of Patient Eligibility

A patient will be considered eligible for admission to the trial when the data forms entitled "Determination of Patient Eligibility" have been completed by one of the doctors responsible for clinical management, and received by the doctor responsible for trial administration.

VIII. Randomization Procedure and Treatment Assignment

Having received the data forms referred to above, the doctor responsible for trial administration will provide the doctor concerned with therapeutic infusions with a schedule, assigning the patient to treatment with high or low dose concentrate, as appropriate.

IX. Prophylactic Administration of Concentrate

Once weekly, the patient will receive an infusion of high or low dose concentrate - depending on which treatment period is current. High dose concentrate will be given in an amount calculated to produce a plasma factor VIII level greater than 5% for 24 hours. Low dose concentrate will be given in an amount calculated to raise the factor VIII level by less than 1%.

The total volume given to an individual patient will be the same throughout the trial. Patients will be told that they are receiving one of two different doses of factor VIII concentrate. Needles used for prophylactic infusions will have an outside diameter no greater than a No. 19 gauge. Precautions will be taken to maintain firm pressure on the infusion site until haemostasis is assured.

X. Treatment for Bleeding Episodes

Treatment with fresh frozen plasma or factor VIII concentrates will be given as required for bleeding episodes, in the usual manner, at the Treatment Centre. In all instances requiring replacement therapy, the patient will be evaluated by one of the doctors responsible for clinical management, and information concerning the bleeding episode and treatment required, will be recorded as detailed in the data forms.

XI. Follow-up Clinical Information

Complete information will be recorded as detailed in the data forms (see Appendix B - 1, 2 and 3), for each of the treatment periods. At the end of each treatment period, the data forms relating to that period will be sent to the doctor responsible for trial administration. The main objective clinical index of progress will be the 'Number of Bleeds'.

Secondly, the total dose of therapeutic material given to the high and low dose groups, and thirdly - the time off school for bleeding episodes in each group.

XII. Follow-up Laboratory Information

At the beginning of each trial period, a factor VIII inhibitor screen (4), will be performed. On at least three occasions during each trial period, the high and low dose concentrate pre-infusion and post-infusion plasma factor VIII levels will be assayed. The therapeutic materials will also require random assay.

XIII. Special Problems

A. Bleeding episode requiring treatment within 24 hours prior to a prophylactic dose

It is anticipated that upon occasion, a bleeding episode will occur shortly before a scheduled prophylactic dose of concentrate. If a bleeding episode occurs which requires treatment within 24 hours prior to the next scheduled prophylactic dose, the administration of that prophylactic dose will be delayed until 24 - 48 hours after the last dose of replacement therapy for the bleeding episode in question. Thereafter, the schedule of administration of prophylactic doses may be adjusted to the convenience of the patient.

XIII (Contd)

B. Development of factor VIII inhibitors

If at any time during the trial, a patient develops inhibitors to factor VIII, this will be noted on the data forms which will be sent to the doctor responsible for trial administration, and the patient will be withdrawn from further participation in the trial.

C. Patients withdrawn from the Trial

Extreme efforts must be made to ensure that, once admitted to the trial, a patient fulfils all the requirements. For a variety of reasons, (e.g., development of factor VIII inhibitors, serious intervening illness, necessity to move out of the country, lack of patient co-operation etc.), it may be necessary to withdraw patients from further participation in the trial. However, it must be realised that at the moment of treatment assignment, patients are - for the purposes of data analysis - irrevocably admitted to the trial. All available information must be sent to the doctor responsible for trial administration, in the event of unavoidable withdrawal. Substitute patients should be considered, if withdrawals take place in the first half of the trial.

REFERENCES

1. NILSSON I. M., BLOMBACK M. & AHLBERG A. (1970) - Our experience in Sweden with prophylaxis in haemophilia
Bibliotheca Haematologica, 34, 111

2. LUJAS O. N. (1970) - Hypnosis and stress in haemophilia
Bibliotheca Haematologica, 34, 73

3. BIGGS R. & MACFARLANE R. G. (1966) - Treatment of Haemophilia and other Coagulation Disorders
Blackwell Scientific Publications, Oxford

4. BIGGS R. & BIDWELL E. (1959) - A method for the study of antihaemophilic globulin inhibitors with reference to six cases.
British Journal of Haematology, 5, 379

HML/2/73