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 trials have, as yet, been carried out to determine whether this aim can be achieved.

The frequency of spontaneous haemorrhage in the past should approach the contemplated frequency of routine administration of factor VIII. Thus initially, only clinically severely affected patients should be incorporated in the 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 would be desirable to control these sources of potential bias by designing a trial with two specific requirements. First, the variation among patients might be controlled by a "switchback design", whereby each patient serves as his own comparison. Secondly, the individual variation of a single patient between placebo and factor VIII might be controlled by employment of a double-blind method. This method would be feasible.

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.

1. Eligibility Criteria

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

1. Age - 7 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.

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* 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.

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 assay (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, and during the other two terms, once-weekly infusions of indistinguishable placebo**.

The designation of these terms as treatment or placebo periods will be made on a random basis. 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.

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. It is hoped that the Medical Directors of Haemophilia Units in the boy's home area will be responsible for obtaining consent for inclusion in the trial.

** The placebo will consist of a hepatitis-free human plasma protein fraction. The manufacturers, IMMUNO of Vienna, from whom we hope to obtain our freeze-dried factor VIII concentrate, have offered to prepare the placebo for us - and will undertake to make its appearances and physical characteristics indistinguishable from the factor VIII concentrate.

2. The physician responsible (Dr. Rainsford) for clinical management will be 'blind' to the treatment assignment. He will determine patient eligibility, complete data forms and decide what treatment is required for bleeding episodes when they occur.

3. The physician responsible (Dr. Aronstam) 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 of random numbers, and inform the physician responsible for therapeutic infusions each term, which patients are to receive concentrate and which, placebo régimes.

4. The physician responsible (Dr. Tomlinson and Staff) for therapeutic infusions, will administer concentrate or placebo to patients. He will give the infusions once weekly.
He will also give therapeutic infusions of factor VIII concentrate when required for a bleeding episode, but s ince he is not 'blind' to the treatment assignment, he must receive instructions about this from the physician responsible for clinical management.

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.
The following points will be made clear:-

1. During the entire trial, each patient will receive an infusion once weekly of either concentrate or placebo.
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 placebo group. He should act accordingly by not taking undue risks, and by promptly reporting symptoms suggesting haemorrhage, as usual.

4. All patients will receive best available treatment, as usual, for bleeding episodes when they occur. Symptoms should be reported promptly, as usual.
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 the physician responsible for clinical management, and received by the physician responsible for trial administration.

VIII Randomization Procedure and Treatment Assignment

Having received the data forms referred to above, the physician responsible for trial administration will provide the physician responsible for therapeutic infusions with a schedule for assigning the patient to treatment with concentrate or placebo, during each of the treatment periods.

IX Prophylactic Administration of Concentrate

Once weekly, the patient will receive an infusion of concentrate or placebo, depending on which treatment period is current. Concentrate will be given in an amount calculated to produce a plasma factor VIII level greater than 5% for 24 hours.

Dr. Aronstam will supervise the preparation of infusions for the trial. The total volume given to an individual patient will be the same throughout the trial, so that the patient will not be given an indication as to whether he is receiving concentrate or placebo. Needles used for prophylactic infusions will have an outside diameter no greater than 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 the physician 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 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 physicians responsible for trial administration (Dr. Arblaster, Dr. Aronstam and Dr. Rosemary Biggs).

XII Follow-up Laboratory Information

At the beginning of each trial period, a factor VIII inhibitor assay (4), will be performed. On at least three occasions during each trial period, the concentrate and placebo pre-infusion and post-infusion plasma factor VIII level will be assayed.

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.

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 physician 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 assure 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 physician 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.

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