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INTRODUCTION

Coagulation Factor VIII and IX concentrates are an absolute requirement for the survival of patients with haemophilia A and B respectively. If made available in sufficient quantities these patients can lead near normal lives.

At the present time these concentrates are obtained from the plasma of human blood donors. The extraction methods used are essentially physico-chemical in nature and thus make it possible for molecular damage or aggregation to arise. The same holds for current procedures designed (heat treatment) to reduce/eliminate viral contamination. A damaged or aggregated molecule may not be fully biologically active and as a consequence its clinical efficacy will be impaired. It may also be cleared rapidly from the circulation and thus the duration of efficacy will be impaired. Aside from influencing in vivo recovery and half-life it has been suggested that aggregates primarily between contaminating proteins (IgG and fibrinogen) in the concentrates, may be responsible for a variety of rarely observed untoward effects associated with the infusion of these coagulation factor concentrates. These include acute pulmonary insufficiency, cerebral siezures, mild and severe generalised allergic reactions and transient anginal pain. This latter complication is relevant to the present difficulties for a Scottish patient experienced retrosternal pain during the trial infusion of an SNBTS factor VIII concentrate (see below).

There are currently no in vitro (laboratory based) methods which allow a manufacturer to be certain that these coagulation factor concentrates will behave normally when injected into a patient. There is the beginnings of a scientific literature which suggests that a haemophilia A dog model may prove to be an acceptable model*, prior to patient exposure of factor VIII concentrates.

*There is no haemophilia A dog colony in the UK. The SNBTS is in the process of discussions with the Glasgow Veterinary School with a view to establishing this facility. Colonies currently

exist in Canada, the Netherlands and the USA. Thus at the present time any significant change in the manufacturing procedures for the production of factor VIII and IX concentrates necessitates the generation of data, derived exclusively from patients, on the in vivo recovery and half-life of the final product and its clinical efficacy.

It should be emphasised that the major and most common complications following the use of factor VIII and IX concentrates is the transmission of live viruses. It seems probable, but not yet proven, that current heat treatment procedures are effective with regard to killing HIV (AIDS) virus. There is insufficient data available to indicate whether these heat treatment procedures will eliminate the non-A, non-B hepatitis virus (NANB) contamination which is probably present in the majority of the batches of factor VIII and IX concentrates prepared from UK derived donor plasma. The acquisition of this data currently represents a major unresolved problem for the NHS plasma fractionators (see below).

PURPOSE OF CLINICAL TRIALS/STUDIES

The studies required to validate a new factor VIII and IX concentrate can be summarised as follows:-

1. Studies required prior to issue for clinical use

   (Type I Studies)

   The first production batches should be studied in at least 6 appropriately selected non-bleeding haemophilia patients. The aim of the exercise is to ascertain whether the in vivo recovery and t/2 life are acceptable (ideally, not significantly different from the product already in use and/or an equivalent commercial product) and that there are no significant untoward clinical effects.

   It should be emphasised that Type I Studies are undertaken on patients who are not bleeding and thus the administration of the product cannot be regarded as part of their treatment.

2. Studies required immediately on completion of Type I Studies

(Type II Studies)

These studies are designed to ascertain whether the product is biologically active in the manner predicted. Information is therefore required, ideally in the surgical context, that the product exerts an acceptable haemostatic effect. Untoward clinical symptoms can also be recorded.

3. Studies requiring long term follow-up of haemophilia patients

(Type III Studies)

These studies should be designed to ascertain whether the virocidal (heat) treatment regimes are effective and whether they produce mild damage to proteins (creating neoantigens) and thus the development of antibodies. Although they should be regarded as a routine prospective monitoring procedure of all haemophilia patients on replacement therapy there is an urgent need for a specialised form of this exercise - the follow-up, using liver function tests on blood samples of patients who receive their first exposure to factor VIII concentrates (these patients are referred to as "virgin" patients). The purpose of this study is to ascertain whether the current heat treatment procedures are effective in eliminating NANB viral hepatitis transmission.

Note: **Type II and III Studies are undertaken following the use of coagulation factor concentrates in the context of the treatment or prevention of active bleeding in patients.**

ASSESSMENT OF RISK

SNBTS records of reported untoward effects following the use of PFC derived products have only been maintained since 1980.

Type I Studies

Since 1980 the SNBTS has initiated 3 Type I studies (maximum 6 patients each). Only one untoward effect has been recorded and on one patient only. During the last study (in 1984/85) an Edinburgh patient

developed retrosternal pain ("angina-like" pain) during the infusion. This caused considerable alarm at the time but the Haemophilia Director (Dr Ludlam) subsequently took the view that this episode was psychosomatic and not related directly to the product - which has been used extensively throughout the SHS ever since.

Since 1979 there have been in excess of 12,000 separate patient exposures to SNBTS factor VIII and IX concentrates. Of these at least 2,000 were associated with heat treated products. All were related to patient treatment regimes. No significant adverse effects have been reported, with the exception that 4 months ago colleagues in Belfast forwarded evidence indicating that a batch of PFC factor VIII appeared to be less biologically active than normal.

It is concluded that the incidence of adverse clinical reactions to SNBTS coagulation factor concentrates is exceedingly small: certainly less than 1/12,000 patient exposures.

Type II Studies

Aside from the recent report from Belfast there have been no other reports of defective biological activity of SNBTS coagulation factor concentrates since 1979, in the context of treating patients without inhibitors. However, there has been another report from Belfast which has suggested that the SNBTS heat treated factor IX concentrate may not be as effective as the unheated product with respect to the management of haemophilia patients with inhibitors.

It is concluded that the risk of loss of biological activity of issued SNBTS coagulation factor concentrates for replacement therapy in patients without inhibitors is negligible.

Type III Studies

Whilst there is currently no evidence of neoantigen development associated with SNBTS heat treated coagulation factor concentrates, this potential problem has not been adequately explored (due to difficulties

in interesting Haemophilia Centre staff in this project). If "allergic" reactions proved to be a clinical manifestation of this proposed phenomenon then the absence of reports associated with heat treated products would suggest this risk is of theoretical interest only.

The risks of virus transmission are not theoretical. Whilst there is every reason to believe that current developments will eliminate the risk of HIV (AIDS) infection it cannot be assumed, at the present time, that this applies to other viruses (notably HBV and NANB). It is not possible to give an assessment of risk with current products. Prior to product heat treatment and HBV vaccination the evidence of HBV and NANB transmission was high - as many as 50% of patients have been reported to have persistent abnormal liver function tests. In a study from Sheffield (UK) 21% of the patients had chronic progressive liver disease, believed to be primarily due to NANB infection.