0422

SEMI-AUTOMATION OF CRYOPRECIPITED FACTOR VIII PRODUCTION.
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The essential processing stages of cryoprecipitate production include plasma-separation, freezing, thawing and harvesting. An automatic cabinet has been developed to perform the freezing and thawing stages according to a predetermined time sequence. Employing conventional refrigeration and operating over a temperature range of -70°C to +30°C, a full cabinet load of 90 bags can be frozen in 30 minutes and thawed in 90 minutes while being rotated in the high air flow. Use of the freeze-thaw cabinet has resulted both in high yield and reproducibility of cryoprecipitates and has permitted increased cryoprecipitate production with energy saving sufficient to offset the capital cost of the equipment.

0423

IN VIVO AND IN VITRO COMPARISONS OF ANTI-INHIBITOR COAGULANT CONCENTRATES (AICC) FOR HEMOPHILIC THERAPY.
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In FVIII:C deficient persons, who also have circulating antibodies to the molecule, replacement therapy with FVIII concentrates elevates the antibody level and is of limited or no value. Treatment with prothrombin complex concentrates, however, has had varying degrees of success in these patients depending on the significance of the bleed.

Currently available Anti-Inhibitor Coagulant Concentrates (AICC), containing factors II, VII, IX, and X in their non-activated as well as activated forms, have been shown to be effective in controlling bleeds in some of these patients.

Two commercially available AICC products and two research preparations were evaluated using conventional in vitro clotting techniques. In vivo assays were also performed in animal systems using the Wessler venous stasis assay. Despite similarities by in vitro assays, striking differences exist in the results obtained using the animal systems. As shown by the Wessler venous stasis assay for in vivo testing, the materials are much more active (at least an order of magnitude) than currently manufactured factor IX concentrates.

In vitro clotting assays that are now available (namely factors II, VII, IX, X, IIa, Xa, NAPTT, FVIII correctional activity, and FVIII inhibitor bypassing activity assays) do not necessarily predict the in vivo efficacy of these AICC products. Furthermore, there is no correlation between the FVIII correctional activity and the FVIII inhibitor bypassing activity assays which are now being used to monitor these preparations.

0424

THE NATURAL HISTORY OF HEMOPHILIC FACTOR VIII-ANTIBODIES: DIFFERENCES IN THE HALF DISAPPEARANCE TIME FOLLOWING ANAMNESTIC RISE.
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In 12 severe hemophiliacs with an antibody to factor VIII of the high responder type antibody activity was followed over a treatment free period of at least three months up to seven years,following 30 factor VIII treatments. After reaching the peak level the antibody titer declined exponentially with a median half disappearance time of 36 days within in a period of 2 - 7 months. There was a considerable variation of the half disappearance time among patients and even in the same patient.Particularly interesting were two patients who showed an unusually short half disappearance time of 5 and 9,5 days,respectively. On the other hand, in one patient the half disappearance time after three stimulations was between 67 and 98 days.

In five patients a biexponential disappearance curve was observed. In these patients after a first component of rapid decline (as described above) a second slower component was observed. The half disappearance time of this second component was between 92 - 480 days (median 200 days). In one patient eventually a plateau was reached. The transition of the first to the second component occured 2 - 7 months after stimulation, when the antibody level had fallen to 2 - 3o % of the peak level. Biexponential curves were observed only in patients with peak levels of more than 300 BU/ml. However, only a single rapid component was observed in one patient with peak levels of 470 BU/ml. Hemophilic factor VIII antibodies are heterogenous with regard to their behaviour in vivo. These differences have to be taken into account if therapeutic decisions have to be made.

0425

AN INHIBITOR SELECTIVELY DIRECTED AGAINST FACTOR VIII-AHF IN A PATIENT WITH VON WILLEBRAND'S DISEASE (vWD).
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We have studied a 17 month old boy with previously diagnosed vWD who presented with intracerebral hemorrhage. There was a history of excessive bleeding from circumcision, after corrective surgery for pyloric stenosis, and from an upper lip cut. He had received multiple units of cryoprecipitate from the first month of life until the present admission. Work-up demonstrated prolonged bleeding time and prolonged PTT, normal prothrombin time, thrombin time, and platelet aggregation with ADP, epinephrine and collagen. Ten days after cessation of factor VIII replacement therapy he had undetectable F VIII-AHF, F VIII-Ag of 86% by the Laurell technique and F VIII-RCo of 18%. We could demonstrate a time-dependent inhibitor directed against F VIII-AHF measuring 92 Bethesda units. In mixing studies with normal plasma, little or nor inhibitory activity directed against F VIII-RCo could be identified. The patient's platelets showed increased ristocetin-induced platelet aggregation (RIPA) at doses as low as 0.5 mg/ml.

There was no evidence of a bleeding disorder in the maternal side of the family. All of the paternal family members studied showed prolonged bleeding times, decreased F VIII-RCo, and increased RIPA with low doses of ristocetin, findings similar to those patients recently characterized as having type IIb vWD. Although other members of the patient's family had previously received cryoprecipitate replacement therapy, no inhibitors appear to have developed in these persons.

Factor VIII inhibitors in vWD are uncommon, with those reported usually showing little or no inhibition of F VIII-AHF. These findings appear to represent a unique pattern of inhibitor development that may be related to a molecular variant of vWD in this patient.