

ORAL ADMINISTRATION OF CONCENTRATED FACTOR VIII OR FACTOR IX PREPARATIONS. N. Sakuragawa, K. Takahashi and I. Horikoshi. Central Clinical Laboratory, Toyama Medical and Pharmaceutical University, Toyama, Japan

In current treatment and prophylaxis of bleeding of the patient of hemophiliacs, purified preparation of coagulation factors is administered intravenously, though some hemophiliacs developed hepatitis and antibody to factor VIII. If we can replenish coagulation factors orally, it will be of great benefit for hemophiliacs.

Materials and methods: (1) Concentrated factor VIII (Concoeight, Green-Cross, Osaka) and factor IX (Konyne, Cutter) were used. (2) Coagulation factors were enclosed in liposomes with addition of aprotinin, and the liposomes were further encapsulated in enteric capsules or suspended in milk to administer orally. (3) Coagulation studies were performed by assaying a-PTT, PT and coagulation assay methods.

Results: (1) A concentrated factor IX preparation (400 units) was given to dogs orally to find raised concentration of factors IX, X, VII and II from 100% to 150%. Konyne contained these factors mentioned above. When 1200 units of Konyne was given in the same way, intravascular coagulation was occurred. These results showed factor IX including factors X, VII and II were absorbed from the intestine. (2) A concentrated factor VIII preparation (100 units) was administered orally to hemophiliacs as volunteers to find raised concentrations of several percentage by biological activity and about 30% by immunological activity. (3) It is absolutely necessary to add aprotinin to prevent proteolysis by the proteases in the gastrointestinal tract in the intestine capsules. One of the absorption mechanism may be due to the fusion of the upper layer membrane of liposome with the gastrointestinal cell.

THE SAFETY OF IBUPROFEN IN FACTOR VIII AND IX DEFICIENT HEMOPHILIACS. M.J. Inwood, B. Killackey, and R.B. Philp. S.W. Ontario Hemophilia Program, St. Josephs Hospital and Department of Pharmacology, University of Western Ontario, London, Ontario, Canada.

Most anti-inflammatory analgesics, particularly ASA, are considered contraindicated in the treatment of hemophiliacs because of inhibition of in vitro hemostatic function. Nevertheless, it would appear reasonable to use such agents in the therapy of chronic or acute hemophilic arthropathy, provided that the anti-inflammatory drug did not increase the incidence of hemorrhage.

Using moderately and severely affected factor VIII and IX deficient hemophiliacs, Ibuprofen was given, using a short (24 hrs) and long term (21 days) trial in order to assess the effect on in vitro hemostasis and the incidence of hemorrhagic symptoms compared to a comparable period prior to the ingestion of drug. An initial safety trial used 24 normal subjects and 12 moderately to severely affected factor VIII and factor IX deficient hemophiliacs. Within each group 600 mgs of Ibuprofen or lactose placebo was given in a random double-blind study. Over 24 hours no changes were seen in the bleeding time, peripheral blood counts or spontaneous bleeding patterns. Subsequently a 21 day trial was initiated with 15 moderately to severely affected hemophiliacs, using a dose of 2400 mg per os Ibuprofen per day. At 0, 7, 14 and 21 days, factor assays, bleeding times, platelet function and cell studies were performed. No clinically significant changes were found in any of the experimental variables, including pattern of spontaneous hemorrhages. Four of the 15 subjects experienced intermittent dyspepsia, controlled by antacids. 7 of 11 individuals with hemophilic arthropathy had a subjective decrease in symptoms from arthropathy.

It is concluded that Ibuprofen is not associated with clinically significant changes in vitro or in vivo hemostatic function in factor VIII or IX deficient hemophiliacs, and should be considered in the treatment of hemophilic arthropathy.

DOSAGE-EFFICACY RELATIONSHIP IN SINGLE-DOSE REPLACEMENT THERAPY FOR ACUTE BLEEDING EPISODES IN HEMOPHILIA A.E. Weiss. Division of Pediatric Hematology, University of Illinois Peoria School of Medicine, Peoria, IL, USA.

The cardinal principle of modern therapy for acute bleeding episodes in hemophilia is "early adequate treatment." To better define "adequate", the dose-efficacy relationship was studied in treatment of 491 acute hemarthroses in 14 adolescent and adult severe hemophiliacs by prompt factor concentrate infusion. All treatments were given within 5 hrs after first recognition of bleeding, with the mean delay being 1.9 hrs; 68% were given within 2 hrs, and 86% within 3 hrs. Treatments were given in 3 concentrate dosage ranges: 8-11, 11-15, and 15-18 u/kg. The outcome of treatment was graded as a "success" (S) if bleeding symptoms resolved promptly without need for additional infusions or absence from school or work; "marginal" (M) if treatment was otherwise successful but rebleeding occurred at the same site within 10 days; or "failure" (F) if symptoms persisted and required additional infusions and/or absenteeism. In each dosage range the time from bleed recognition until treatment and the concentrate dosage were not significantly different among the outcome groups. However, there was a highly significant difference ($p < 0.01$) in the efficacy of treatment at dosage ranges. Similarly, the frequency of rebleeding decreased with increasing dosage for primary treatment. The 10% failure rate with low doses is in agreement with several reports advocating low doses for early treatment, but the higher success rates and lower failure and rebleeding rates with the higher doses indicate that these parameters and their impact on overall bleeding frequency and concentrate usage must be considered in the determination of "adequate" doses.

Dosage (u/kg)	n	S	M	F	Outcome
8-11	159	60%	30%	10%	the 3 dosage ranges (see table). The success rate increased stepwise, and the failure rate decreased, with increasing dosage ranges.
11-15	214	71%	21%	8%	
15-18	118	83%	13%	4%	

MEASUREMENT OF INHIBITORS TO PROCOAGULANT FACTOR VIII (VIIIIC) BY IMMUNORADIOMETRIC ASSAY (IRMA).

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Antibodies against VIIIIC (VIIIICAg) were assayed using a modification of a two-site solid phase IRMA for factor VIII clotting antigen (VIIIICAg). Anti-VIIIICAg antibodies obtained from a multi-transfused haemophilic were separated as IgG and labelled with 125 I. This was used to test plasma from patients with factor VIII inhibitor by competitive binding to common antigenic sites on immunoimmobilised VIIIIC. A haemophilic inhibitor assessed as 225u by the Bethesda method was used as standard. Results of inhibitor assay using the IRMA in 19 plasma samples from 15 severe haemophiliacs were similar to those obtained by the coagulation method. The increased sensitivity by IRMA of 0.01 u/ml enabled measurement of a haemophilic inhibitor undetectable by clotting assay. Anti VIIIICAg activity was also detectable in plasmas from three individuals with acquired inhibitors against VIIIIC. These plasmas which also had measurable residual VIIIICAg gave dilution curves non-parallel to the standard haemophilic plasma curve. Measurement of haemophilic inhibitors using three IRMAs each employing different 125 I labelled haemophilic anti VIIIICAg antibodies showed that there was no difference in the sensitivity of the three assays but in some plasmas the results were discrepant indicating different specificities of the labelled antibodies.