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Prophylactic Therapy in Classical Hemophilia:
A Preliminary Report

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PROPHYLACTIC therapy in classical hemophilia (Factor VIII deficiency) has been unsatisfactory because it is necessary to administer large volumes of plasma at frequent intervals. Since Pool and Shannon[1] described the preparation of a high-potency concentrate of antihemophilic globulin, named cryoprecipitate, concentrated preparations of Factor VIII have become more readily available. Pool, Welton and Creger[2] reported that the administration of this cryoprecipitate intramuscularly was ineffective and resulted in local hematoma formation. The purpose of the present study was to determine: (a) whether it was feasible for a hemophilic patient and his family to administer cryoprecipitate intravenously at home, (b) whether cryoprecipitate administered once or twice daily would prevent spontaneous bleeding and bleeding from minor trauma and (c) whether a correlation could be established between the Factor VIII levels achieved on the two prophylactic regimens and the clinical events during the two periods.

Methods and Materials

The cryoprecipitate derived from ±250 ml. of fresh plasma contains ±70% of Factor VIII activity of the plasma. Because of variations in the Factor VIII content of the starting plasma, individual cryoprecipitates will contain variable amounts of Factor VIII. No attempt was made in this study to select cryoprecipitates which contained the same amount of Factor VIII.

Case Report

J.W., aged 19 years, has severe classical hemophilia with a Factor VIII level of 1%, and has been under our care for the past 15 years. In the six months preceding this study, he had been admitted to hospital on 15 occasions to control various hemorrhagic episodes, mostly hemarthroses of different joints. For three days, Factor VIII levels[3] were determined seven times a day (6.30 a.m., 7.00 a.m., 11.00 a.m., 2 p.m., 6.30 p.m., 7.00 p.m. and 11.00 p.m.). During the next six days, Factor VIII levels were determined at the same times, and the patient was given one unit of cryoprecipitate intravenously at 6.45 a.m. and 6.45 p.m. His mother was trained to prepare and administer the cryoprecipitate during this six-day period. After nine days of hospitalization, he was discharged with a stock of cryoprecipitate,* administration sets and scalp vein needles,† with instructions to administer one cryoprecipitate every 12 hours. The cryoprecipitates were stored in a freezer at home.

At the end of three months he was readmitted to the hospital for a three-day study of the effect of one daily administration of cryoprecipitate given at 6.45 a.m. Blood for Factor VIII assays was collected at the same times as have already been outlined. For the following three-month period, he received one cryoprecipitate daily at home.

Results

Clinical Results: Since the start of this regimen, this patient has not required hospitalization for bleeding episodes. He has attended school on a regu-

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lar basis for the first time in his life. During the first three months, while receiving one cryoprecipitate twice daily, he sustained trauma (minor car accident, falls on the ice) without hematoma formation. The patient volunteered that he was free from the frequent episodes of muscle soreness familiar to persons with severe hemophilia.

During the second period of three months (one cryoprecipitate daily) the patient had hemarthroses on three occasions; he stated that he had more minor discomfort in various muscles during this period than in the first period. These episodes did not require hospitalization; on three occasions the dose of cryoprecipitate was increased to twice per day for two days. The bleeding manifestations then subsided promptly.

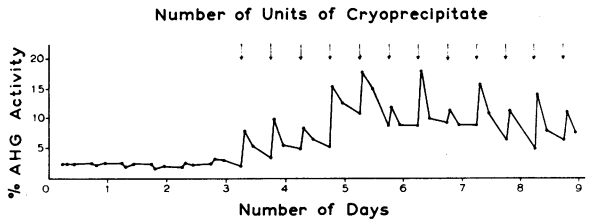

Fig. 1.—Factor VIII levels in J.W. on no treatment (0 to 3 days) and on two cryoprecipitates daily (3 to 9 days).

Laboratory Results: Fig. 1 shows the Factor VIII levels for nine days at the start of the program. During the first three days no cryoprecipitate was administered in order to establish a baseline Factor VIII level. No significant change in Factor VIII levels was shown at various times of the day. From day 3 to 9, one unit of cryoprecipitate was given intravenously every 12 hours. The patient's Factor VIII levels increased rapidly to ±10%, where they were maintained for the next five days. Random assays when he was an outpatient, while on a two-unit regimen, showed that he maintained this level for the next three months.

Fig. 2 illustrates the patient's Factor VIII level for a three-day interval at the beginning of the second three-month period. On day O, the Factor VIII level was in the 10 to 15% range, but quickly decreased to an average of 4% on one unit of cryoprecipitate per day. A similar level has been found on random assays during the past three months.

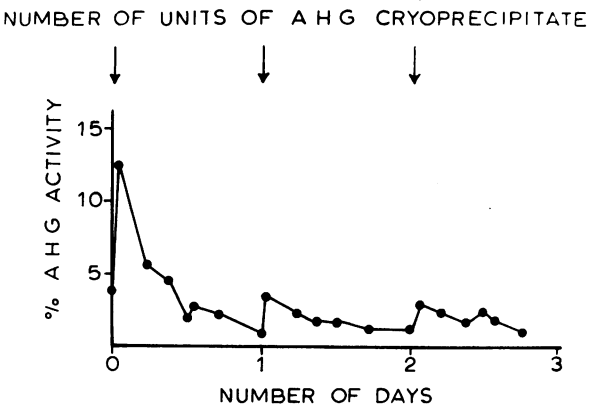

Fig. 2.—Factor VIII levels in J.W. on one cryoprecipitate daily. (AHG = antihemophilic globulin.)

DISCUSSION

Administration of one cryoprecipitate every 12 hours resulted in a sustained Factor VIII level of ± 10%, compared to the untreated level of 1%. Associated with this change in Factor VIII level, the patient was able to attend school regularly and to sustain minor trauma without bleeding. Elevation of the Factor VIII levels to ± 4% by the administration of one cryoprecipitate daily may have decreased spontaneous bleeding, but the patient did sustain spontaneous joint hemorrhages and minor muscle discomforts. It is probable that he would have been admitted to hospital on two occasions had it not been possible to increase the frequency and amount of cryoprecipitate administered at home at these times.

His clinical course during the first three months was similar to that of those members of other kindreds in our hemophilic group who have Factor VIII levels in the range of 5 to 10%. These patients are rarely hospitalized and have hemarthroses only with known trauma.

We have not tested other dosage schedules. It is possible that the administration of larger amounts of cryoprecipitate every morning to achieve higher initial levels might be effective for 24 hours. As more potent Factor VIII preparations become available, satisfactory prophylactic schedules, with increasing intervals between the infusions, should be effective.

The cost of the materials during the first three-month period (exclusive of cryoprecipitate) is $1.50 per infusion, or $270.00 per three-month period. If it is assumed that he would have required seven hospitalizations averaging four days each during this period, the cost, at standard ward rates, would have been $1120.

From the observations made in this patient, the following tentative criteria for instituting a program of prophylactic therapy with cryoprecipitate are proposed:

1. The patient must have severe Factor VIII deficiency.
2. The patient and his family must be able to understand and carry out the technical procedures.
3. Superficial veins must be readily accessible.
4. A physician familiar with the program should be available at all times.
5. An adequate source of cryoprecipitate must be available.

The possibility that prophylactic therapy with cryoprecipitate might stimulate production of circulating anticoagulants has been considered. Because the severe hemophiliac receives such frequent intermittent treatment with Factor VIII preparations, we do not believe that the frequency with which anticoagulants develop should be increased by continuous administration.

Summary Prophylactic therapy in classical hemophilia was evaluated using intravenous Factor VIII concentrate—cryoprecipitate—for a period of six months. The subject was a 19-year-old hemophiliac. Factor VIII assays were made at regular intervals during three periods in hospital. In the first three-day period, during which no concentrate was given, a baseline for Factor VIII level was established. Subsequently, two prophylactic regimens were tried: (1) One unit of cryoprecipitate was given every 12 hours for three months at home, and (2) one unit of cryoprecipitate was given every 24 hours for the following three months. During the first period no hemorrhages occurred, despite minor trauma. In the second period, spontaneous hemarthroses occurred on three occasions. Criteria are proposed for the use of prophylactic therapy in classical hemophilia.

Résumé L'emploi du Facteur VIII—cryoprécipité concentré—sous forme intraveineuse pendant une période de six mois permet de juger le traitement prophylactique de l'hémophilie classique. Le sujet était un hémophile de 19 ans. Pendant trois séjours à l'hôpital, on a procédé à des essais du Facteur VIII à intervalles réguliers. Durant la première période de trois jours—sans administrer de concentré—on a établi une base de départ pour l'étude de l'effet du facteur VIII. Ensuite on a procédé à l'essai de deux traitements prophylactiques: (1) on a administré une unité de cryoprécipité toutes les douze heures pendant trois mois lorsque le malade était chez lui; puis (2) une unité de cryoprécipité toutes les vingt-quatre heures pendant les trois mois suivants. Pendant la première période on n'a pas noté la présence d'hémorragies malgré des traumatismes mineurs. Durant la deuxième période, on a noté la présence d'hémarthroses spontanées à trois reprises. Les auteurs suggèrent des règles pour l'emploi du traitement prophylactique de l'hémophilie classique.

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