Poor Response to Danazol in Hemophilia

By Carol K. Kasper and A. Lois Boylen

We gave danazol (600 mg/day orally for 14 days) to eight adults with mild or moderate hemophilia A, one with severe hemophilia A, and one with moderate hemophilia B. In the patient with severe hemophilia A, the levels of factor VIII two to four days after an infusion of factor VIII concentrate were higher than expected, suggesting a prolonged half-life. In one patient with mild hemophilia A, a questionable slight increase in factor VIII was noted at the end of the study. No change was seen in factor levels of other subjects. Therapy was terminated early, at eight days, in a patient who developed severe muscle cramps, and at ten days in a patient with a severe rash. Another patient developed hepatic dysfunction three days after completing the 14-day trial. In this trial, the side effects of danazol outweighed its meager and questionable benefits.

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RESULTS

A full 14-day course of danazol was completed by eight patients. Two patients terminated danazol after the eighth and tenth day of treatment, respectively, because of untoward side effects. The total number of blood samples obtained ranged from six to nine in patients completing the trial, and from four to five in patients terminating the trial early (Table 1). Assays of a plasma sample performed on three different days were similar; the average difference of any one assay on one day from the mean of three assays on three days was 0.0055 factor VIII μ/mL. Day-to-day variation in factor VIII levels within each subject is expressed by the CV and SEcv, given in Table 1. The CVs of assays on repeated plasma samples of the same patient, assayed on the same day, were higher (mean, 11.1%; range, 7.7 to 19.4%, excluding patient “B”) than those of our reference plasmas, which have average-normal levels of VIII:C and are assayed on different days, and thus are not truly comparable.

No changes in factor levels were seen in the patient with hemophilia B nor in six of those with mild to moderate hemophilia A. One of the latter terminated therapy after eight days. The remaining patient, “C,” with mild hemophilia A (baseline factor VIII:C level

In June 1983, Gralnick and Rick reported that danazol, an attenuated androgen, given in a dosage of 600 mg/d for 14 days, raised factor VIII or IX levels in four patients with hemophilia A and one with hemophilia B. Baseline factor levels of 1% to 5% rose to 3% to 14%. The initial increase usually was observed five to six days after the initiation of therapy and peaked between seven and 14 days. No untoward effects of the drug were seen.

We were intrigued by the possibility of improving factor levels in hemophiliacs without the use of plasma products and the attendant risk of transmission of donor infection. We attempted to duplicate the results of the above study, without success.

MATERIALS AND METHODS

Permission to study the effect of danazol in hemophilia was obtained from the Institutional Review Board of Orthopaedic Hospital and from the Office of New Drug Evaluation of the National Center for Drugs and Biologics. Participating patients signed an informed consent.

We selected ten unrelated young adult patients who did not require plasma products often, were in good general health, and were reliable. One patient had hemophilia B with 2% plasma factor IX, one had severe hemophilia A with less than 1% plasma factor VIII:C, and eight had moderate or mild hemophilia A with plasma factor VIII:C levels of 3%, 6%, 6%, 7%, 8%, 10%, and 12%, respectively. Immediately after one baseline blood sample for clotting factor assay was drawn, each patient was given sufficient danazol to take 600 mg/d for 14 days, and was asked to return every other day for factor assays. Patients were instructed to treat any intercurrent hemorrhages with their usual plasma products. Logs were kept of each dosage of danazol or a plasma product, each blood sample, and any adverse reactions, and patients were questioned about adherence to the protocol by one of the investigators at each clinic visit for blood sampling.

Venous blood was collected by a two-syringe technique. After a good venipuncture was secured with a 21-gauge scalp-vein needle and small syringe, and 2 to 3 mL of blood was withdrawn and discarded, a fresh syringe was attached and blood was withdrawn for assay. Blood was mixed in a 9:1 ratio with balanced citrate anticoagulant and immediately centrifuged at 4° C and 12,000 g for ten minutes. Each plasma sample was divided into several plastic vials and stored at −70° C for up to four weeks before assay. All vials, tubes, syringes, and pipettes in contact with blood or plasma were plastic.

At the completion of the trial, all plasma samples from a given patient were assayed for factor VIII:C on three different assay days. The results of assays of one sample on three assay days were averaged. The samples were not coded, but the technician was not aware of the purpose or details of the study. We used a one-stage assay based on the activated partial thromboplastin time, in which plasma from a patient with severe hemophilia A serves as substrate. Two commercial reference plasmas for factor VIII:C, with levels in the normal range, each were tested on 21 assay days during the time this study was conducted. The coefficient of variation (CV) and standard error of the CV (SEcv) were 6.5, 1.0, and 8.4, 1.3, respectively.

From the Department of Medicine, University of Southern California School of Medicine, and Hemophilia Treatment Center, Orthopaedic Hospital, Los Angeles.

Address reprint requests to Dr Carol K. Kasper, Orthopaedic Hospital, 2400 South Flower St, Los Angeles, CA 90007.

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of 7%) had assays trending upward over time with a plasma VIII:C of 10% by day 13. We have no true control to judge the error of the assay at this level, but the CV of assays of patient “C”’s plasma, 9.4, was the highest of those observed in patients with comparable factor VIII levels, exceeding the CV plus 2 SE of all comparable patients. The high CV suggests a true control to judge the error of the assay at this level, but of the half-disappearance time of infused factor VIII level was 3%, whereas it was predicted to be less than 1%. By day eight, it had returned to less than 1% and thereafter remained at the baseline level. (Our predictions were based on an observed mean eight-and-one-half-hour half-disappearance time in eight previous studies of factor VIII concentrate infusion in this patient.) Thus, this patient appeared to have a brief increase in plasma factor VIII:C or prolongation of the half-disappearance time of infused factor VIII:C.

Six patients reported adverse effects. One patient who felt irritable and two who were drowsy were able to complete the course of treatment, but the latter two men said that they would not be willing to use the drug again. A patient who developed severe muscle cramps on the sixth day stopped the drug after the eighth day; the cramps continued for three more days. The patient with severe hemophilia A developed a marked generalized pruritic maculopapular rash on the eighth day of treatment and discontinued the drug after the tenth day.

The patient with mild hemophilia who had a questionable rise in plasma VIII:C by the end of the study developed hepatic dysfunction. He had no prior history of clinical hepatitis, but his serum had contained antibody to HBsAg since first tested in 1973. At the start of the study, his serum SGOT and SGPT were normal. He felt well on danazol during the study period. On the last day of the study, he bruised his shoulder with a rifle while hunting and required cryoprecipitate. Three days later he noted nausea, malaise, and dark urine. He did not report to us for three more days. By that time, he was jaundiced and had a tender liver edge. Over the next five days, the serum SGOT peaked at 384 IU/L, the SGPT at 680 IU/L, the alkaline phosphatase at 130 IU/L, and the total bilirubin at 5.1 mg/dL. The BUN, serum creatinine, and blood cell counts were normal. Heterophile tests for mononucleosis remained negative. He did not develop antibody to hepatitis A. When jaundice began, the
titer of antibody to cytomegalo virus was 1:32, a low but positive value, but a month later no antibody could be detected. He recovered quickly.

We wondered if he could have had hepatitis non-A non-B. He had received cryoprecipitate five months prior to the danazol trial and on the last day of the study, but at no time between those doses. The intervals between those two doses of cryoprecipitate and the onset of his symptoms are not typical of hepatitis non-A non-B. We conclude that his episode of liver dysfunction is unexplained but may have been caused by danazol.

DISCUSSION

Danazol in a dosage of 600 mg/d for a period of up to 14 days was associated with elevations of plasma factor VIII:C in only one or two of ten patients. In one patient, the early transient rise might be due to prolongation of the half-life of infused factor VIII. In the other, a slightly higher level at the end of the treatment period might be due to the onset of liver dysfunction or might have been within the error of the assay. Thus, we have no clear evidence that danazol directly stimulated endogenous factor VIII:C production in our patients.

In contrast to these meager and uncertain benefits, moderate to serious medical problems arose in three patients and mild problems in another three patients. We assume that these problems were related to the ingestion of danazol. Thus, in our group of ten patients with hemophilia, the risks far outweighed the benefits.

Our results obviously differ greatly from those reported by Gralnick and Rick. Although the characteristics of both subject groups appear to be similar, the number of patients studied is small. Perhaps a few patients with mild or moderate hemophilia are responsive to danazol, and the group studied by Gralnick and Rick was composed, by chance, of such individuals. Responsiveness to danazol might be characteristic of particular genetic variants of mild and moderate hemophilia. Another possible source of dissimilar responses to a drug in two apparently identical protocols is variation in the characteristics of the drug from one batch to another. We have no evidence, however, of any such variation in danazol.

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REFERENCES

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