The Use and Safety of Ibuprofen in the Hemophiliac

By Martin J. Inwood, Barbara Killackey, and Shirley J. Startup

After demonstrating initial safety of Ibuprofen administered to hemophiliacs, a 16-wk double-blind individual crossover trial was designed to test the safety and, to a more limited extent, the efficacy of 1600 mg of Ibuprofen or placebo given daily to 20 hemophiliacs with hemophilic arthropathy. The trial was completed with no evidence of increased frequency or severity of hemophilic bleeding episodes or clinical or laboratory evidence of bleeding secondary to Ibuprofen. There were five treatment failures, none associated with hemorrhage or lack of compliance. A benefit was obtained in reduction of early morning stiffness and pain. Ibuprofen should be considered as a safe and potentially beneficial antiinflammatory agent in the treatment of carefully monitored hemophiliacs eligible for such therapy.

hemophiliac. arthropathy is a common complication of severe and moderately affected factor-VIII and factor-IX-deficient hemophiliacs. It usually involves a lengthy process consisting of pain, joint stiffness, decrease in range of motion, muscular atrophy, and a final stage of a nonfunctional joint. It is, without doubt, one of the major problems of hemophilia now that appropriate factor replacement is available to treat acute hemorrhage.

Acetylsalicylic acid (ASA), a common antiarthritis, antiinflammatory agent, is contraindicated for the treatment of hemophilic arthropathy because of its known affects in hemophilia, in particular, its long-term affect on platelet function. In contrast to ASA, we have shown that the antiinflammatory agent Ibuprofen (Motrin, Upjohn, Kalamazoo, Mich.), produces only short-term reversible effects on platelets. A safety trial performed by us in which hemophilic males received 2400 mg of Ibuprofen for 21 days showed no adverse effects of the drug on the hemostatic processes. Subsequently, Hasiba et al. and Thomas et al. have concluded that Ibuprofen represents a safely effective agent for the management of hemophilic arthropathy in a select group of hemophilic patients.

The purpose of this trial was to study the effects of Ibuprofen on hemophilic arthropathy in a larger group of hemophiliacs for a longer period of time, using a double-blind, randomized crossover trial design.

MATERIALS AND METHODS

Subjects

Twenty severely or moderately affected factor VIII or IX individuals between the ages of 17 and 40 yr were selected on the basis of all having one or more joints showing a significant degree of hemophilic arthropathy, who had received three consecutive comprehensive annual assessments, and who were known to be reliable and compliant individuals on the basis of past clinic attendance and daily diary compliance. At the outset of the trial, nine had severe symptoms, six minor symptoms, and five no daily symptoms of arthropathy. All had changes in joint range of motion and muscle mass. A complete assessment of musculoskeletal, laboratory, physical, psychosocial, systems review, and coagulation factor use was performed prior to the trial. After a detailed explanation of the trial, accompanied by a letter, an informed consent was obtained under the authority of the University of Western Ontario and St. Joseph's Hospital, London, ethics review committee.

Medication

A randomized double-blind crossover trial was used, with each subject receiving 1600 mg Ibuprofen (4 x 400 mg), or identical lactose placebo (Upjohn Company, Don Mills, Ontario). Crossover occurred at 8 wk, the alternate medication used for a further 8 wk, for a total of 16 wk. Medication was taken prior to each meal and before retiring at night. All subjects took no medication (except factor replacement) for a washout period of 2 days prior to the start of the trial. During the 4-mo trial, only carefully monitored acetaminophen and codeine were allowed for the relief of pain.

Tests Performed

Each subject was evaluated at weeks 0, 4, 8, 12, and 16. Blood was withdrawn just prior to drug administration on day 1 for control levels, then approximately the same time of day at weeks 4, 8, 12, and 16. Using standard hematologic techniques, the hemoglobin, hematocrit, leukocyte, platelet, erythrocyte, and reticulocyte counts and prothrombin time were performed using batch processing in a conventional hospital laboratory. Creatinine, SGOT, SGPT, alkaline phosphatase, albumin levels, and a standardized Ivy bleeding time, were performed on each person on day 1, week 8, and week 16.

Stool occult blood tests, using the Hemoccult II Dispense Packs (Smith, Kline and French), were performed at weeks 0, 4, 8, 12, and 16. Serum Ibuprofen levels were performed at the same intervals.

Musculoskeletal Evaluation

At every clinical evaluation, a standard musculoskeletal protocol was performed on each subject by one investigator (S.S.). Particular attention was given to the range of motion, frequency, and duration of morning stiffness, pain, and crepitus in affected joints. All joints

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were tested, with emphasis given to the knees, ankles, and elbows and other target joints. Musculoskeletal symptoms were graded on a daily basis, using an objective scale.

**Records**

Each subject was required to keep a daily diary of bleeding episodes, with the amount of factor concentration transfused and acetaminophen or codeine taken for the relief of pain. These records were part of their regular therapy surveillance program, which included reporting all unusual symptoms or signs on a daily basis, e.g., dyspepsia, change of stool color, unusual bleeding, or bruising.

**Statistical Analysis**

The data obtained was combined for the 8 wk on Ibuprofen and compared to the 8 wk on placebo. Subsequent analysis used paired t testing and variance analysis.

**RESULTS**

Of the initial 20 subjects enrolled in the study, 5 withdrew before completion because of treatment failures. One because of persistent dyspepsia while on Ibuprofen and 4 due to lack of relief from musculoskeletal symptoms. These 4 subjects, prior to the trial, had all been ingesting between 900 and 2400 mg of Ibuprofen daily for pain and disability due to arthropathy; 3 withdrew while on placebo and 1 withdrew while on Ibuprofen. The one subject who withdrew while on Ibuprofen had, prior to the trial, been taking up to 2400 mg of Ibuprofen daily for arthropathy involving 9 major joints.

Table 1 shows the hematologic data from the trial, with no statistical differences found between the Ibuprofen or placebo time periods. The decreases in hemoglobin, hematocrit, and erythrocyte count while on Ibuprofen were, on average, lower than on placebo, but the decreases were within diurnal and experimental error. No concomitant increase in reticulocytes and consistently negative stool occult blood tests and normal bleeding times ruled out significant hemorrhage or hemolysis. No significant differences were shown in the biochemical tests.

The number of bleeding episodes and the amount of factors VIII and IX concentrate used in association with the number of bleeding episodes did not change significantly during the trial. An additional 7586 U of factors VIII and IX were required during the 8 wk on placebo, compared to the 8 wk on Ibuprofen. No abnormal patterns of bruising or bleeding were noted. No major life-threatening hemorrhages occurred.

The amount of acetaminophen or codeine taken for analgesia during the first 4 wk on Ibuprofen was significantly lower than the amount taken during the first 4 wk on placebo. However, this degree of significance was not sustained when the 8-wk period on Ibuprofen was compared to the same period on placebo.

The musculoskeletal results showed no significant change in the range of motion of joints throughout the trial, whether on placebo or Ibuprofen. However, both the frequency and duration of morning stiffness was significantly decreased ($p < 0.003$) while on Ibuprofen when compared to the 8 wk on placebo. The frequency of morning stiffness was decreased by 36.5% and the duration of morning stiffness was decreased by 55.7% while on Ibuprofen (Table 2).

Of the 9 subjects who had severe symptoms of arthropathy, 6 (67%) had good relief with Ibuprofen, 2 (22%) felt worse while on Ibuprofen, and 1 (11%) had no change throughout the trial. Of the 6 subjects that had minor symptoms of arthropathy, 2 (33%) had relief while on Ibuprofen, 1 (17%) felt worse while on Ibuprofen, and 3 (50%) noticed no change. Six months after completion of the study, 8 of the subjects, all with severe symptoms, were taking regular daily Ibuprofen, and 7 were taking intermittent courses of relief of acute symptoms and morning stiffness.

**DISCUSSION**

It has been our experience that individual hemophiliacs often have considerable difficulty in distinguishing between the symptoms of synovitis/arthritis and hemorrhage. The study was not able to demonstrate the factor concentrate-sparing ability of Ibuprofen, and this will probably only be demonstrated using a longer

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pretreatment</th>
<th>Ibuprofen First 4 wk</th>
<th>Ibuprofen Second 4 wk</th>
<th>Placebo First 4 wk</th>
<th>Placebo Second 4 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>15.2 ± 0.2</td>
<td>14.8 ± 0.3</td>
<td>14.2 ± 0.3</td>
<td>15.4 ± 0.3</td>
<td>15.2 ± 1.0</td>
</tr>
<tr>
<td>Hematocrit %</td>
<td>45.1 ± 0.7</td>
<td>43.7 ± 1.0</td>
<td>42.2 ± 0.9</td>
<td>45.6 ± 0.9</td>
<td>45.2 ± 0.8</td>
</tr>
<tr>
<td>RBC (× 10^6/μl)</td>
<td>5.1 ± 0.1</td>
<td>5.0 ± 0.1</td>
<td>4.8 ± 0.8</td>
<td>5.2 ± 0.2</td>
<td>5.2 ± 0.1</td>
</tr>
<tr>
<td>WBC (× 10^3/μl)</td>
<td>6.1 ± 0.5</td>
<td>6.1 ± 0.4</td>
<td>5.8 ± 0.5</td>
<td>6.2 ± 0.4</td>
<td>6.1 ± 0.5</td>
</tr>
<tr>
<td>Platelets (× 10^3/μl)</td>
<td>240 ± 13</td>
<td>238 ± 15</td>
<td>238 ± 15</td>
<td>229 ± 14</td>
<td>234 ± 20</td>
</tr>
<tr>
<td>Reticulocytes (per μl)</td>
<td>77,266 ± 8,638</td>
<td>64,286 ± 6,764</td>
<td>79,558 ± 6,945</td>
<td>67,615 ± 6,716</td>
<td>70,714 ± 7,676</td>
</tr>
<tr>
<td>Bleeding time (min)</td>
<td>3.25 ± 0.2</td>
<td>—</td>
<td>2.92 ± 0.3</td>
<td>—</td>
<td>3.22 ± 0.3</td>
</tr>
</tbody>
</table>

Mean ± SEM, n = 15.
HEMOPHILIA AND IBUPROFEN

Table 2. Effects on Musculoskeletal Function

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ibuprofen</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of early morning</td>
<td>42.2 ± 9.6*</td>
<td>95.2 ± 14.1†</td>
</tr>
<tr>
<td>stiffness (min/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency of morning stiff-</td>
<td>21.6 ± 4.5</td>
<td>34.1 ± 4.2</td>
</tr>
<tr>
<td>ness (days/test period)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* p < 0.003 compared with placebo.
† Mean ± SEM, n = 15.

period of testing and a larger patient group with active hemarthropathy.

While Ibuprofen did not alter the range of motion in the joints tested, significant decreases in the frequency and duration of joint stiffness were demonstrated. Morning stiffness is a common symptom of hemophilic arthropathy, and any decrease will improve mobility, assist in rehabilitation, and improve the lifestyle of affected hemophiliacs. These results are in agreement with those of Hasiba and Thomas.4,5 Similarly, although Ibuprofen was not rated as significantly reducing analgesic use, our clinical assessment has been that by reducing the degree of discomfort and stiffness, the use of more potent analgesics can be avoided.

The bleeding time has an important role in the acceptability of an analgesic/antiinflammatory agent in hemophilia. If it is not pathologically prolonged, it will probably be suitable for use in hemophilia.7 Eyster et al.8 have demonstrated unexplained prolonged bleeding times in hemophiliacs. In addition, these workers demonstrated that 3 of 8 hemophiliacs receiving either Ibuprofen or indomethacin in undisclosed amounts as therapeutic agents had prolonged bleeding times. Thomas et al.,4 in their study of 8 hemophiliacs receiving Ibuprofen, did not show prolongation of a template bleeding time, the same method used by Eyster’s group. Deykin9 demonstrated potentiation of the bleeding time if the individual was concurrently ingesting ethanol and Ibuprofen, and Haire10 a similar prolongation with concurrent use of two antiinflammatory agents. In this series of previous studies and daily clinical experience, we have not been able to demonstrate a significant prolongation of the bleeding time using a standardized controlled depth incision IV testing, with the exception in a factor VIII deficiency with thrombocytopenia. All our patients were carefully monitored for excessive alcohol use, other medications, and the bleeding time was performed by one worker.

No evidence for bleeding was obtained during this trial. During the 4 yr Ibuprofen has been used in this program for hemophiliacs with arthropathy, three gastrointestinal hemorrhages have occurred. One due to the concomitant use of ASA; another with an associated thrombocytopenia; and lastly, with persistent dyspepsia and alcohol. Ibuprofen has not been given to individuals under the age of 16 yr. These observations would agree with the observations of Thould et al.11

We conclude from this trial that Ibuprofen can be used safely and provide a benefit for carefully monitored hemophiliacs with significant symptoms of morning stiffness and discomfort secondary to hemophilic arthropathy. Whether the use of Ibuprofen will reduce the rate and degree of progression of hemophilic arthropathy and decrease the frequency and amount of factor concentrate transfusions for affected joints remains to be proven.

REFERENCES

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