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Danazol Therapy in Hereditary Angioedema

Lawrence C. Sweet, MD,* Charles E. Jackson, MD,** Sam S. Yanari, PhD,* and J.B. Yott, RN**

Hereditary angioedema (HAE) is an autosomal dominantly inherited condition in which a deficiency of the inhibitor (C1Inh) of the activated first component of complement is associated with recurrent episodes of edema of the skin, gastrointestinal tract, and larynx. The pituitary gonadotropin inhibitor, danazol, has been reported to be effective in preventing attacks and increasing C1Inh levels. Our experience with 11 patients from five kindreds corroborated those results and has revealed that most patients can be maintained symptom-free on 100-200 mg of danazol daily. Side effects were minimal, although one young woman discontinued therapy because it aggravated her acne. The elevation of C1Inh levels and prevention of HAE attacks provide evidence that danazol is the present drug of choice in treating this genetic disease.

Fig. 1

Biochemical Indications of HAE

Although the biochemical hallmark of this disease has been known since 1963 (2), the precise mechanisms responsible for edema formation are not entirely clear. In addition to its function as an inhibitor of the activated first component of complement, which can result in asphyxiation. Deaths from airway obstruction have ranged from 6% to as high as 54% in some series of patients (5-6). Although the biochemical defect can be demonstrated in infancy, several years usually elapse before typical attacks of edema begin. About half of patients have symptoms by age 7 years, and two thirds by age 13. Once established, attacks may vary from one or less per year to several per month.

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complement, C1Inh also acts as a control factor in the fibrinolytic- and kinin-generating systems (7-8). C1Inh deficiency, therefore, can result not only in uncontrolled complement activation, but also in the production of bradykinin from high molecular weight kininogen via the unopposed activity of plasma kallikrein. Activation of the complement cascade results in the production of active fragments (C3a and C5a) from the third and fifth components of complement known as anaphylatoxins. Anaphylatoxins can cause direct release of the edema-inducing mediator histamine from tissue mast cells. Bradykinin, on a molar basis, is as potent as histamine in inducing tissue edema. Although 24-hour urinary histamine levels and plasma bradykinin levels are both elevated during acute attacks, the major edema-inducing factor is now felt to be a fragment of the second component of complement (C2) known as C2 kinin (9).

**Diagnosis**

The specific diagnosis of HAE is generally made by the determination of serum C1Inh levels by immunodiffusion. In the common form of this disorder, levels average 20% of normal. However, in the variant form of the disease with normal or elevated levels of inactive C1Inh, the specific diagnosis must be made by a functional assay of the capability of the patient's C1Inh to inhibit esterase activity (10). Since the biochemical hallmark of HAE is unopposed activity of the activated first component of complement, decreased levels of its natural substrates, C2 and C4, should result (11-13). Below-normal concentrations of C4 have been uniformly found in all patients with HAE. Furthermore, serum C4 levels appear to follow the natural course of the disease, dropping during attacks of edema and then rising, but to subnormal levels, during symptom-free intervals. Since C4 levels are easily determined by a simple immunodiffusion analysis available in most clinical laboratories, this test serves as a useful screening procedure for suspected cases. C1Inh levels can also be determined by immunodiffusion, but the test is not widely available (14). Functional assay of esterase-inhibiting capacity is available only in a few specialized laboratories. Determination of C2 levels is difficult, and the values do not parallel the course of the disease as well as C4 levels.

**Forms of Drug Therapy**

Treatment of acute attacks of edema with such drugs as epinephrine, antihistamines, and corticosteroids has long been known to have questionable effectiveness (5). This is perhaps not surprising if the major edema-inducing agent is indeed a fragment of C2. The administration of fresh plasma is controversial—although it provides a source of C1Inh, it also provides an ample supply of C4 and C2 and may, therefore, lead to the further production of edema-inducing factors (15-17). The availability of purified C1Inh in sufficient quantities should result in more satisfactory treatment of acute episodes in the future. At present, patients with airway edema must be monitored quite closely, since tracheostomy may be necessary.

Although treatment of acute attacks still leaves much to be desired, some success has been achieved with drug therapy designed to prevent the frequency and severity of attacks. The knowledge that the complement, fibrinolytic, and kinin generating systems were intimately interrelated led to trials of the plasmin inhibitor, epsilon aminocaproic acid (EACA) (18-20). It clearly was effective in diminishing attack frequency, but the large quantities required (7-15 gms per day) and unpleasant side effects (muscle necrosis is the most severe) make it difficult to use on a regular basis (4). A more effective drug of similar activity, tranexamic acid, was found to induce neoplasms in experimental animals and has not, therefore, been released commercially (21).

Testosterone was first used to treat HAE under the mistaken impression that it was a histamine inhibitor in man (22). In spite of the lack of such activity, the drug was clearly effective in reducing the frequency of attacks. Since side effects precluded long-term therapy in children and women, attention in recent years has focused on the so-called impeded androgens.

**Effectiveness of danazol**

Danazol (danocrine, Sterling-Winthrop Co, Rensselaer, NY), a derivative of ethinyltestosterone, is one such drug which has been shown to be effective in HAE (23-25). It is mildly anabolic but has markedly attenuated androgenic potential. Because it produces a dose-dependent reduction of serum gonadotropins, it results in a concomitant decrease of the primary sex hormone. The drug does not appear to produce significant virilization in women or any change in potency in men. Most patients note slight weight gain and all women have some menstrual irregularity, the majority becoming amenorrheic after about three months of treatment. This latter effect has led to the widespread use of this drug in the treatment of endometriosis.

Treatment of HAE patients with androgenic hormones results in an extremely interesting biochemical effect. Within five days of starting treatment, serum levels of C1Inh increase. Levels rarely reach normal but are sufficient to allow the return of serum C4 levels to normal. This effect is accompanied by a clearcut diminution in the frequency and severity of HAE attacks (23-29). It appears, therefore, that androgens allow at least partial correction of the biochemical defect by stimulating an increased production.
of the normal gene product. However, the precise mechanisms by which this is accomplished are unclear.

Clinical Trials

We used danazol to treat 11 individuals from five different kindreds, mostly from two previously reported kindreds (30). The 11 patients, six women and five men, ranged in age from 16 to 71 years. Clinically, all had had typical HAE attacks involving skin and gastrointestinal tracts for at least five years. In addition, six had experienced significant airway edema, including one whose severe episodes prompted a permanent tracheostomy.

After we obtained serum for baseline determination of C1Inh and C4 levels, complete blood count (CBC), urinalysis, and automated laboratory screen (SMAC), the patients were begun on danazol 200 mgm twice daily for two months. Laboratory studies were repeated at two weeks and again at the end of the two-month period. In an attempt to ascertain the minimum effective dose, danazol dosage was then reduced by 50 mg twice daily at two-month intervals; laboratory studies were again repeated at the end of each interval. Patients were monitored for frequency and severity of HAE attacks and, if it appeared that a lower than optimal dose of danazol had been reached, the dosage was increased. Once an apparently effective dose had been determined, it was maintained for the rest of the study period.

Results

Results are recorded in Table I. Patients 5 and 6, who had the highest levels of C1Inh and C4 levels near the lower end of the normal range, were both receiving testosterone. Patient 1, also on testosterone, had a C1Inh level one third of normal, but low C4. As anticipated, danazol induced a modest increase in C1Inh levels which was, however, sufficient to allow abnormally low C4 levels to rise. As a group, C1Inh levels increased from an average of 17% to 36% of normal, while C4 rose from an average of 63% of normal to the middle of the normal range. A decrease in the frequency of HAE attacks also accompanied these changes.

No significant virilizing effects were noted in the six women in the study, although one did discontinue treatment after three months because it exacerbated pre-existing facial acne. All female patients experienced amenorrhea regularly on the initial high dosage. Transient, minimal microscopic hematuria was seen in several patients but did not persist. No significant alterations were noted on CBC or biochemical screening determinations.

Figure 2 details the course of one of the patients over almost a two-year period. There was a prompt increase in C1Inh to an average of twice the pre-treatment level. Although the C1Inh remained well below the lower normal limit of 16 mg/dl, C4 levels promptly rose to normal values. This patient had three HAE attacks during the course of treatment (designated by arrows), all of which occurred

### Table I

<table>
<thead>
<tr>
<th>Pt</th>
<th>Sex</th>
<th>Age</th>
<th>Previous RX</th>
<th>C1Inh* before RX</th>
<th>C4** before RX</th>
<th>Attacks before RX</th>
<th>Max C1Inh after RX</th>
<th>Max C4 after RX</th>
<th>Attacks after RX</th>
<th>Minimal Effective Dose of Danazol</th>
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<tr>
<td>1</td>
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<td>23</td>
<td>3</td>
<td>Methyl-Testosterone</td>
<td>5</td>
<td>6</td>
<td>4/mo</td>
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<td>19</td>
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<td>F</td>
<td>23</td>
<td>17</td>
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<td>&lt;6</td>
<td>1/2-3 mo</td>
<td>17</td>
<td>18</td>
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<td>1/mo</td>
<td>14</td>
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<td>54</td>
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<td>10</td>
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<td>1/mo</td>
<td>11</td>
<td>47</td>
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<td>14</td>
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</tr>
<tr>
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<td>F</td>
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<td>—</td>
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<td>***</td>
<td>***</td>
</tr>
<tr>
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<td>1/mo</td>
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<td>5</td>
<td>1-2/mo</td>
<td>7</td>
<td>29</td>
<td>0/9 100 mg/d</td>
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</tbody>
</table>

* C1Inh Normal — 16-34 mg/ml
** C4 Normal — 13-75 mg/dl
*** Dropped out of study
when the dose of danazol had been decreased to 100 mg daily. The attacks were accompanied by a fall in serum C4 levels, while the level of C1Inh did not precisely parallel the clinical course of the disorder.

Conclusions
Our experience with 11 patients, for a total 243 patient-months of treatment, confirms the efficacy of danazol in HAE. The documented use of serum C1Inh levels suggests that the major pharmacologic effect of danazol is to allow increased production of the "good" gene product. Increased C1Inh activity then results in decreased serum complement activation (as evidenced by a return of C4 levels to normal) and a diminution in the frequency and severity of HAE attacks. The effectiveness of the drug appears to be dosage dependent. In our group, 100-200 mg per day was generally adequate.

In comparison to previously available treatment modalities, danazol was generally well tolerated. Only one patient discontinued the drug because of side effects. Alternative dosage schedules (such as every other day) may allow even better patient acceptance without sacrificing therapeutic effectiveness. It is also quite likely that additional drugs, with even more attenuated androgenic potential, will be developed and will provide even safer therapy for all HAE patients regardless of age or sex.

Acknowledgments
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