
Hereditary angioedema: a current state-of-the-art review, V: attenuated androgens for the treatment of hereditary angioedema

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Objective: To provide a summary of the literature regarding the use of attenuated androgens during the past 40 to 50 years for the treatment of hereditary angioedema (HAE).

Data Sources: MEDLINE and PubMed were searched to identify studies involving the treatment of HAE with androgens.

Study Selection: Studies were selected based on their relevance to the use of androgens for the treatment of HAE.

Results: Attenuated androgens have proven successful for the short- and long-term treatment of HAE. Adverse effects are still concerning, and their use in children and pregnant women must be undertaken with great caution. Scheduled monitoring of liver function tests and lipid profiles in patients treated with these medications is critical.

Conclusions: Attenuated androgens have been successful in the short- and long-term treatment of HAE, and they are still the most frequently used medications in the United States for the treatment of this disease. There is a lack of readily available options for the treatment of acute HAE attacks apart from the administration of fresh frozen plasma or safe prophylactic therapies; however, several appropriate agents currently in clinical trials in the United States appear promising.

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INTRODUCTION

The management of hereditary angioedema (HAE) must address the abrogation of acute episodes of angioedema and short- and long-term prophylaxis.^{1,2} Unfortunately, there are no drugs approved to date in the United States for the treatment of acute episodes,¹ although many are in clinical trials and nearing Food and Drug Administration (FDA) approval. C1 inhibitor concentrate has been available for many years in Europe and Canada but is not yet available in the United States. Attenuated androgens are used for the treatment of acute episodes and have been used for short- and long-term prophylaxis for many years. The adverse effects of the attenuated androgens have often been of concern. The newer, synthetic, 17- α -alkylated androgens, such as danazol, stanozolol, and oxandrolone, have milder adverse effects and have, therefore, been used more frequently in recent years. These drugs are less virilizing than the older drugs, such as methyltestosterone,³ but like all attenuated androgens must be administered with care to children and pregnant or lactating women.^{4,5}

Treatment regimens in many of the previously published studies of attenuated androgens typically started with high doses of androgens and tapered down the dose every few

weeks until the lowest maintenance dose that provided symptom control was reached. Alternatively, treatment with lower doses can be initiated with a progressive increase of the dose until symptoms are controlled and adverse effects are minimized. The initial reports of attenuated androgens in the treatment of HAE were accomplished despite a poor understanding of the actual pathophysiology of the disease and mechanism of action of these medications. During the past several decades, attenuated androgens have been shown to increase C1 inhibitor^{2,6} and C4 levels.⁷ However, the precise mechanism by which androgens lead to an increase in C1 inhibitor and C4 levels remains unclear.⁸

Major contraindications to attenuated androgen therapy include pregnancy, lactation, prostate cancer, and childhood. Potential adverse effects include increased hair growth, weight gain, seborrhea, acne, deepening of the voice, vasomotor symptoms, decreased breast size, menstrual irregularities, decreased libido, hepatic necrosis (peliosis hepatis), cholestasis, hepatic neoplasms, hypertension, and abnormal lipoprotein metabolism.⁹ Attenuated androgens have been successful in the short- and long-term treatment of HAE, and they are still the most frequently used medications in the United States for the treatment of this disease. This review provides a summary of the literature regarding the use of attenuated androgens during the past 40 to 50 years for the treatment of HAE.

METHYLTESTOSTERONE

Methyltestosterone is one of the oldest available synthetic anabolic steroids and is derived from testosterone. Testosterone is an androgen but is not methylated and, therefore, has not been useful in preventing attacks of HAE.¹⁰ Methyltes-

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tosterone is responsible for the development and maintenance of primary and secondary male sex characteristics. Adverse effects include elevation of liver enzymes, acne, gynecomastia, increased aggression, and water retention. Methyltestosterone is sold in a sublingual form for faster absorption for the treatment of conditions other than HAE but is also available in an oral tablet and capsule form. Current FDA indications for the use of methyltestosterone include primary hypogonadism, hypogonadotropic hypogonadism, and metastatic breast cancer.

The first report in the literature of methyltestosterone for the treatment of HAE comes from Spaulding in 1960.¹¹ He empirically treated one family with presumed HAE and noted an improvement of their symptoms. His explanation was that methyltestosterone led to thickening of collagen fibers and, thus, prevented swelling. We now know that this is not the mechanism by which methyltestosterone leads to a decrease in attacks of angioedema.

Seventeen years later, 4 male patients with HAE were treated with 10 mg of methyltestosterone daily in a double-blind, crossover fashion.¹² These 4 patients had only 4 episodes of angioedema during a total of 46 months of methyltestosterone treatment compared with 19 episodes during 11.8 months of treatment with placebo ($P < .001$). In addition, the 4 attacks during methyltestosterone treatment were reportedly less severe than attacks occurring during the placebo phase. This study further evaluated serum C4 levels and found that mean (SD) levels increased from 84 (21) $\mu\text{g/mL}$ to 176 (36) $\mu\text{g/mL}$ during methyltestosterone treatment. Adverse effects from methyltestosterone treatment in this study included mild nausea and 1 episode each of increased creatine phosphokinase levels and prostatitis. Liver function test results remained stable in these patients.

DANAZOL

Danazol is a synthetic analogue of ethinyltestosterone and was first developed in 1963. Danazol was first marketed as Danocrine but has since become available as a generic drug. It is available only as an oral capsule in doses of 50, 100, and 200 mg. It was the first drug the FDA approved for the treatment of endometriosis. Danazol is now also FDA approved for the treatment of fibrocystic disease of breast and HAE. Danazol is metabolized by the liver and should not be used by patients with underlying liver disease.

The first study of danazol in decreasing the frequency and severity of HAE attacks was not published until 1976.¹³ Each patient served as his or her own control. There was only 1 attack among 46 courses of danazol compared with 44 attacks among 47 placebo treatments. Although the exact mechanism of action remained unclear, danazol increased C1 inhibitor and C4 serum concentrations. The changes in C1 inhibitor and C4 levels were seen within a few days and rapidly decreased once danazol therapy was discontinued. This effect was believed to be correlated directly to the dose of danazol used.¹⁴

A few years later, Hosea et al¹⁵ reported the successful long-term treatment of 69 patients with HAE with danazol, but described significant adverse effects, including weight gain, myalgias, headaches, microscopic hematuria, abnormal liver function test results, alopecia, menstrual irregularities, virilization, dizziness, and vomiting. They suggested periodic monitoring of patients receiving danazol therapy and downward titration of the dose. These concerns were confirmed by several subsequent studies,^{16,17} but the drug's efficacy seemed to outweigh these risks, especially if the dose was limited to the minimal dose effective for symptom control.

Retrospective data confirm that danazol should be avoided during pregnancy.¹⁸ Women exposed to danazol during pregnancy were identified from individual case reports. Of the 94 completed pregnancies, 23 resulted in virilized females. These adverse effects did not occur if danazol therapy was discontinued before the eighth week of pregnancy. Although more common with higher doses, virilization was reported in 1 case with a 200-mg/d dosage.

More recently, danazol has been reported to have an increased risk of early atherosclerosis.¹⁹ Although there were no significant differences for total cholesterol or triglyceride levels, patients with HAE receiving danazol were at 11.6 times increased risk for reduced high-density lipoprotein concentration and 4.4 times increased risk for elevated low-density lipoprotein concentration. Current recommendations strongly suggest regular monitoring of liver function test results and lipid levels when treating patients with danazol.

OXYMETHOLONE

Oxymetholone is an anabolic steroid first developed in 1960 and known to increase the production and excretion of erythropoietin and to stimulate erythropoiesis.²⁰ Because of its effect on erythropoiesis, oxymetholone is currently FDA approved for the treatment of acquired aplastic anemia, anemia of chronic renal failure, Fanconi anemia, and pure red cell aplasia. Serious adverse effects have been reported, including cholestatic jaundice, hepatic necrosis, and malignancy. Also, there is significant concern for premature epiphyseal closure with the use of oxymetholone in children. Oxymetholone is available only as an oral tablet.

The success of oxymetholone therapy in decreasing the frequency and severity of attacks was first reported in 1974.²¹ These results were confirmed in a group of 6 women during a total of 204 patient-months.²² Adverse effects of daily oxymetholone therapy reported included depression, mild elevations in serum creatine phosphokinase levels, menstrual irregularities, and weight gain.⁷

Subsequently, Sheffer et al⁷ reported the use of oxymetholone for the treatment of HAE in a group of 16 patients while trying to establish a low dosage schedule for this medication. Of the 16 patients, 15 had no further attacks during treatment with 5 mg of oxymetholone daily. The last patient required a dose of 10 mg/d to prevent any further attacks. Treatment for 13 of the asymptomatic patients was decreased to 5 mg every other day. Of these 13 patients, 6

remained attack free, whereas the other 7 had mild attacks. This study demonstrated that daily oxymetholone therapy decreased attacks and increased C1 inhibitor function and C4 protein concentration and function.^{6,23} More important, Sheffer et al⁷ provided evidence that alternate day therapy decreased the adverse effects of oxymetholone while still protecting patients from HAE attacks.

STANOZOLOL

Stanozolol, first developed in 1959, is an anabolic steroid also known by the brand name Winstrol. It is only FDA approved for the treatment of HAE. Stanozolol is supplied as 2-mg oral tablets. Stanozolol also has substantial fibrinolytic properties and has been effective in the treatment of Raynaud phenomenon and cryptofibrinogenemia.²⁴ Stanozolol has also been used successfully in treatment of AIDS wasting syndrome.²⁵ Several reports document abuse by athletes to help build muscle mass, boost acceleration, and recover faster from workouts, as exemplified by the Olympic sprinter Ben Johnson, who tested positive for the drug in 1988 and was stripped of his gold medal and world record in the 100-meter race.

Because of stanozolol's 30:1 anabolic-androgenic ratio,²⁶ low toxicity, and low cost, Sheffer et al²⁷ further evaluated stanozolol for the treatment of HAE. They first administered stanozolol to patients with HAE in 1977 with the goal of using an attenuated androgen that was effective while minimizing adverse effects. In 1987, they published their 10-year experience of stanozolol treatment in 37 patients (23 female and 14 male patients aged 9–73 years). Patients began receiving 1 to 2 mg of stanozolol daily, and the dose was slowly tapered if the HAE remained adequately controlled. Acute attacks were treated with a burst of 4 mg of stanozolol every 6 hours until resolution, often in conjunction with fresh frozen plasma. After the acute attack, a dose was reduced back to 2 mg/d and again tapered as tolerated.

After 10 years, 20 patients required maintenance therapy, ranging mainly from 1 to 2 mg/d or less, and 17 patients were tapered off treatment. The most common adverse reactions reported were related to hepatic dysfunction, with weight gain, hirsutism, and menstrual irregularities observed to a lesser extent. An update of the response to stanozolol treatment in these patients after 20 to 40 years of follow-up has recently been published.²⁸ The data from this study suggest that stanozolol can be used safely for short- and long-term prophylaxis at the minimum doses required to control attacks in HAE. Regular monitoring of liver function test results is still recommended.

ATTENUATED ANDROGENS IN THE PEDIATRIC POPULATION

The adverse effects of the attenuated androgens, including virilization and decreased growth rates,^{29,30} have led to their cautious use in the treatment of HAE in prepubescent children. Farkas et al³¹ recently published their experience treating children with HAE. Danazol was administered for short- and long-term prophylaxis in 11 children. Initial doses of 100

to 200 mg/d were used and titrated down to 100 mg every 2 to 3 days after 6 months only if the child was in clinical remission. The bone age, skeletal growth, and weight development of these patients were not substantially different from the age-expected normal values. Hirsutism was not observed with these doses of danazol. Only 1 case of delayed menarche and irregular menses was reported. Similarly, an 8-year-old boy was successfully treated with danazol at a dose of 200 mg every other day with no evidence of hormonal imbalance during an 11-month follow-up period.³²

Oxandrolone is a synthetic anabolic steroid with reported minimal virilizing adverse effects and an acceptable safety profile and, therefore, has been used in a variety of pediatric conditions.³³ Oxandrolone was administered at a dose of 0.1 mg/kg per day in a 6-year-old boy with life-threatening HAE. Treatment resulted in a marked decrease in attacks of angioedema and concurrent normalization of C4 levels. However, early signs of virilization were reported.³³ These studies only further affirm the goal of using the lowest dose possible to control symptoms in prepubescent children. This permits successful use of attenuated androgens to prevent attacks of angioedema in children while minimizing worrisome adverse effects. With close observation and monitoring, attenuated androgens can be safely used in the pediatric population.³¹

CONCLUSIONS

Attenuated androgens have proven successful for the short- and long-term treatment of HAE. Adverse effects are still concerning, and their use in children and pregnant women must be undertaken with great caution. Scheduled monitoring of liver function test results and lipid profiles in patients treated with these medications is critical. Patients should be treated with the lowest dose of attenuated androgens needed to maintain symptom control. Pharmacies can compound attenuated androgenic drugs, such as stanozolol, in dosages of 1 to 2 mg. We still lack readily available options for the treatment of acute attacks, apart from the administration of fresh frozen plasma, but several appropriate agents in current clinical trials hold significant promise and we hope will be available in the United States shortly.

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