

Hereditary angioedema: Safety of long-term stanozolol therapy

David E. Sloane, MD, Chyh Woei Lee, MD, and Albert L. Sheffer, MD *Chestnut Hill, Mass*

Background: Attenuated androgens control attacks of hereditary angioedema. Short-term studies of such patients treated at our institution with attenuated androgens demonstrated no adverse effects. However, the side-effect frequencies in patients receiving long-term treatment are relatively less well characterized.

Objective: To assess the frequencies of various side effects of the attenuated androgen stanozolol in a population of patients with hereditary angioedema treated for 20 to 40 years.

Methods: Data on side effects in patients who continued stanozolol therapy since 1987 were obtained by means of questionnaire. Patients were evaluated by physical examination; biochemical assays of hepatic function, serum lipids, and prostate specific antigen; and liver ultrasound.

Results: The minimal initial effective dosage of stanozolol was 0.5 to 2.0 mg daily, although most patients achieved symptomatic control and decreased the dose and frequency as the frequency of attacks decreased. Treatment-related symptoms developed in 10 of 21 patients. No interruption in stanozolol therapy was required because symptoms subsided with a reduction in the stanozolol dosage. Adverse side effects included hirsutism, weight gain, menstrual irregularities or postmenopausal bleeding, acne, and mood changes. Liver enzyme assays revealed no persistent abnormalities. Liver ultrasounds in 8 patients revealed 3 abnormalities deemed unrelated to therapy. Five patients had a reduced high-density lipoprotein, and 2 patients had elevated triglycerides.

Conclusion: Stanozolol is a safe and effective drug for the long-term management of hereditary angioedema.

Clinical implications: Stanozolol may be used in the long-term treatment of patients with hereditary angioedema provided such patients are closely supervised with routine clinical, biochemical, and radiologic assessments. (*J Allergy Clin Immunol* 2007;120:654-8.)

Key words: Hereditary angioedema, attenuated androgens, stanozolol, side effects

Abbreviations used

HAE: Hereditary angioedema
PSA: Prostate specific antigen

Prophylactic administration of androgens^{1,2} or anabolic agents with impeded androgenic effects³⁻⁵ clearly prevents spontaneous as well as soft tissue trauma (dental and surgical)-induced episodes of angioedema in patients with hereditary angioedema (HAE). Since Spaulding's¹ original report of the efficacy of methyltestosterone in HAE, several anabolic agents with impeded androgenic effect have been used in the treatment of this disorder.³⁻⁵ Biochemical evidence in support of therapy with such agents includes the partial correction of the decreased inhibitor to the first complement component (C 1 INH) serum concentration and reversal of the secondarily depressed C4 serum levels.³ Attenuated androgens probably enhance hepatic C 1 INH production. Because these drugs act on the liver, hepatic dysfunction as a result of treatment is a concern.⁶⁻⁸

With close supervision of patients with HAE treated with attenuated androgens, the anticipated adverse side effects such as retarded growth in children, virilization, hepatic dysfunction, and lipid abnormalities have not been observed in short-term assessments.^{8,9} A previous study determined the lowest and safest dosage, which controlled the symptoms of patients with HAE by using oxymetholone and then stanozolol.⁹ The current study retrospectively ascertained the clinical status of patients with biochemically proven HAE who continued androgen therapy since our last report^{9,10} and also evaluated the frequency of adverse effects of such therapy. Along with assessment of treatment-related symptoms, biochemical assays of hepatic function, serum lipids, liver ultrasound, and prostatic assessment by prostate specific antigen (PSA) were performed. The patients had been followed by the investigators for at least 20 and in some instances for nearly 40 years.¹⁰

METHODS

A previous study from this institution documented a decade of experience with stanozolol in the treatment of 37 patients with HAE.¹⁰ The purpose of the current study was to evaluate those patients in follow-up, including physical and biochemical assessment, to define any long-term toxicity of therapy with attenuated androgens. Of the original group, 2 patients with HAE have died (1 of natural

From Harvard Medical School/Brigham and Women's Hospital.

Disclosure of potential conflict of interest: A. L. Sheffer has consulting arrangements with Genentech and Pharming and has received grant support from Dyax. D. E. Sloane has received grant support from GlaxoSmithKline and Dyax and is on the speakers' bureau for Genentech and Novartis. C. W. Lee has declared no conflict of interest.

Received for publication March 22, 2007; revised June 5, 2007; accepted for publication June 29, 2007.

Reprint requests: Albert L. Sheffer, MD, Harvard Medical School/Brigham and Women's Hospital, Division of Rheumatology, Immunology, and Allergy, 850 Boylston Street, Suite 540, Chestnut Hill, MA 02467. E-mail: asheffer@partners.org.

0091-6749/\$32.00

© 2007 American Academy of Allergy, Asthma & Immunology
doi:10.1016/j.jaci.2007.06.037

TABLE I. Population data for patients with HAE*

Patient no.	Sex	Current age (y)	C1INH (functional/nonfunctional)	Medication initiated			Years on stanozolol
				MT	Oxy	Stan	
1	F	57	Functional		1976	1977	29
3	M	73	Functional	1974	1976	1977	29
4	F	61	Functional		1976	1977	29
5	F	48	Functional		1976	1977	29
6	F	55	Functional		1976	1977	29
7	F	48	Functional		1976	1977	29
8	M	72	Nonfunctional	1968	1976	1977	29
9	M	66	Nonfunctional	1973	1976	1977	29
10	F	72	Functional	1968		1977	29
14	M	63	Functional		1976	1977	29
15	M	54	Functional		1976	1977	29
16	F	58	Functional			1977	29
17	F	31	Functional			1983	23
18	F	42	Functional			1979	27
19	M	70	Functional		1976	1977	29
21	M	58	Functional	1967	1976	1977	29
22	F	59	Functional		1976	1977	29
26	F	84	Functional			1977	29
28	F	45	Functional			1977	29
30	F	62	Functional			1977	29
36	M	88	Functional		1976	1977	29

F, Female; M, male.

*Patients with HAE from our institution treated with attenuated androgens participated in the current study on the safety of stanozolol. Patient numbers are not consecutive because they are carried over from reference 9 and experience summarized in reference 10. Before the initiation of stanozolol (*Stan*), 5 patients had been taking methyltestosterone (*MT*), and 14 had been taking oxymethalone (*Oxy*).

causes unrelated to HAE and the other of esophageal carcinoma), 2 brothers were lost to follow-up, and 5 were using a drug other than stanozolol (danazol). As previously reported, a significant proportion of patients with HAE whose disease is controlled with attenuated androgens see a decrement in the frequency and/or severity of their attacks. In keeping with this, 6 of the 37 patients no longer required pharmacologic treatment for HAE. The remaining 22 patients reported on are those who have been treated with stanozolol since 1977. They received a questionnaire approved by the Brigham and Women's Hospital Human Study Committee (Table I). Of the 22 reported patients, 2 patients had biochemical documentation of a nonfunctional C 1 INH, whereas the remaining 20 had subnormal concentrations of C 1 INH.

The reported population consisted of 9 men and 13 women from 31 to 88 years of age, mean 60.3 years, who without treatment experienced at least monthly attacks of HAE. Most of the patients had been asymptomatic for several months to years on stanozolol therapy. Fifteen patients were followed at the Brigham and Women's Hospital Allergy Section every 6 months. The other 7 patients had returned to their respective primary care physicians or had moved from the area, but they responded to the study questionnaire. Patients were evaluated by the investigator every 6 months unless abnormalities were detected on assessment, in which case the patient was asked to return in a month. The objective was to maintain the patients with HAE attack-free at a dosage of stanozolol that did not cause hepatic enzyme elevation. Patients receiving stanozolol (usually at 2 mg per day or less) had a complete blood count, liver enzyme measurement, lipid profile, and PSA for men measured every 6 months. Patients underwent routine breast and prostate examination by their primary care physician, gynecologist, or urologist. This and all previous protocols were approved by the Brigham and Women's Hospital Committee for the Protection of Human Subjects from Research Risks. Informed consent was obtained from each participant.

RESULTS

Clinically relevant treatment-related symptoms occurred in 10 patients, but these adverse reactions (symptoms) required no interruption in stanozolol therapy and subsided with a reduction in the dosage of stanozolol (Table II). The most commonly reported adverse effects included hirsutism (7 patients), weight gain (3 patients), menstrual irregularities (oligomenorrhea in 2 patients and menorrhagia in a third patient) or postmenopausal bleeding (4 women), acne (3 patients), and mood changes (2 patients). None of these effects was long-lasting or required specific treatment. As patients achieved improved control of their HAE and were able to decrease the dosage of stanozolol, these symptoms resolved without permanent sequelae. There were 11 patients who experienced no adverse effects with stanozolol therapy (Table II).

Measurement of liver enzymes (alanine aminotransferase, aspartate aminotransferase) within the past year revealed no persistent abnormalities (Table III). Hepatic ultrasound recently has been suggested as an additional parameter for routine assessment of adverse effects of attenuated androgens involving the liver, because hepatic function and transaminase levels may be preserved in some patients with hepatocellular adenoma.¹¹ A recent HAE consensus report supports this position.¹² Therefore, liver ultrasound evaluation was performed after this recommendation was published. Recent scans in 8 patients revealed 3 with abnormalities. One occurred in a patient with esophageal carcinoma, but this patient

TABLE II. Patient-reported side effects of stanozolol*

Patient no.	Sex	Current stanozolol dose	Menstrual cycle	Hair growth	Skin	Weight gain	Psychiatric	Voice	Other	None reported	No survey
1	F	2 mg Q4 d								Yes	
3	M	1-2 mg QD								Yes	
4	F	1 mg QOD		Yes							
5	F	PRN								Yes	
6	F	PRN		Yes	Yes						
7	F	2 mg QD		Yes (thinner)	Yes (oily)		Loss of libido	Deeper			
8	M	PRN								Yes	
9	M	1-2 mg Q3 d				Yes					
10	F	2 mg QOD		Yes		Yes					
14	M	1 mg QD								Yes	
15	M	2 mg × 2 d, off for 1 d		Yes		Yes	“Short temper, anger”				
16	F	PRN								Yes	
17	F	1 mg QD	Yes	Yes							
18	F	1 mg QOD vs 2 mg QOD	Yes		Yes (acne)						
19	M	PRN								Yes	
21	M	2 mg QOD								Yes	
22	F	PRN	Yes								
26	F	2 mg QD		Yes							
28	F	PRN									X
30	F	PRN								Yes	
36	M	PRN								Yes	
Total patients		Totals	3	7	3	3	2	1	0	10	
21			13	21	21	21	21	21	21	21	
Men	Women										
8	13										

F, Female; M, male; Q4 d, every 4th day; QD, daily; QOD, every other day; PRN, as necessary; Q3 d, every 3rd day; 2 d, daily for 2 days; 1 d, off the 3rd day.

*Patients with HAE reported the side effects of stanozolol treatment via standardized questionnaire. See text for details. Patient numbers are not consecutive because they are carried over from reference 9 and experience summarized in reference 10.

subsequently had a normal abdominal computed tomography (CT) scan, suggesting that the liver lesion was inconsequential. A second patient had fatty infiltration of the liver, and a third had evidence of slight steatosis without a mass. A fourth patient had a small hemangioma that was considered unrelated to therapy.

Lipid profiles demonstrated no patient with either elevated total cholesterol or low-density lipoprotein (LDL) cholesterol. There was a reduced high-density lipoprotein (HDL) in 5 patients and elevated triglycerides in 2. Clinical evidence of cardiovascular complications was not observed in this study. An elevated PSA occurred in 1 of the 5 men tested.

Decisions regarding stanozolol dosage were based on the frequency and severity of a patient's HAE attacks according to an empirically successful weaning protocol (Fig 1). The initial dosage of stanozolol was 2 mg once daily. At the time of this assessment, 5 patients were on stanozolol therapy (1-2 mg) daily, 4 were on alternate day therapy, 3 patients were on less frequent but regular therapy, and 9 patients were no longer taking stanozolol regularly after being asymptomatic for at least a 3-month period. These patients used stanozolol only as needed preoperatively or for cutaneous or gastrointestinal attacks (as

necessary). For dental extraction and for other procedures involving soft tissue trauma and/or general anesthesia, stanozolol 4 mg was administered every 6 hours for 5 days before to the procedure.¹⁰ To break an acute attack, 2 units of fresh frozen plasma were administered (as has recently been reviewed¹³), and the patient was told to take stanozolol 4 mg 3 times daily if it was early in an attack. Thereafter, the 2 mg per day schedule was resumed and a reduction in dosage schedule attempted according to the weaning protocol (Fig 1). The severity of the attacks was clearly reduced while on stanozolol and even after regular stanozolol therapy was discontinued.¹⁰ As noted previously, the mean concentration for C4 rose when the patients were receiving a maintenance dosage.⁹ In some cases, the C4 reached the normal range, but the C 1 INH levels did not reach the lower range of normal on maintenance therapy.²

DISCUSSION

The objectives in treating HAE include the amelioration of acute attacks and the prevention of spontaneous

TABLE III. Biochemical data*

Sex	Hepatic enzymes (U/L)		Lipids (mg/dL)			
	ALT (normal = 7-52)	AST (normal = 9-30)	Total cholesterol (normal = 140-240)	LDL (normal = 50-160)	HDL (normal = 35-60)	Triglycerides (normal = 40-160)
F	14	18	209	ND	ND	176
M	30	30	136	79	21	182
F	29	27	215	159	44	60
F	15	18	146	ND	ND	57
F	24	24	191	125	47	96
F	13	16	226	ND	ND	133
M	ND	ND	ND	ND	ND	ND
M	ND	ND	ND	ND	ND	ND
F	15	18	109	42	42	127
M	56	28	171	120	25	129
M	25	20	144	89	41	69
F	20	22	178	110.2	59	44
F	29	24	130	76.4	47	33
F	19	39	130	82	31	23
M	29	25	ND	ND	ND	ND
M	30	29	224	155	38	160
F	14	19	191	88	57	126
F	23	19	158	112	22	118
F	8	13	192	ND	ND	70
F	15	16	167	ND	ND	53
M	16	28	148	97	32	135
No. elevated	<u>1</u> 19	<u>1</u> 19	<u>0</u> 18	<u>0</u> 13	<u>5</u> 13	<u>1</u> 18

F, Female; M, male.

*The most recent laboratory results for the patients with HAE using stanozolol. ND indicates that the test was not done or that no documented results could be obtained. See text for details. Patient numbers are not consecutive because they are carried over from reference 9 and experience summarized in reference 10.

episodes as well as attacks induced by soft tissue trauma (eg, dental extraction or surgery). Several drugs are currently available for such therapy. These include anti-fibrinolytic agents (ϵ -amino caproic acid), fresh frozen plasma, and anabolic steroids (stanozolol, danazol). Other agents such as a kallikrein inhibitor, a bradykinin 2-receptor antagonist, recombinant rabbit C 1 INH, and pasteurized human C 1 INH are being studied and may be available in the United States in the near future.

The administration of methyltestosterone^{1,2} and attenuated androgens such as oxymetholone,⁴ danazol, and stanozolol^{5,9,10} reduces the incidence and severity of spontaneous attacks of HAE. Although the efficacy of the anabolic steroids in the treatment of HAE is well established, the mechanism for this effect remains unclear. Stanozolol is metabolized in the liver and with its administration, there appears to be an enhancement of C 1 INH protein production.⁹ However, the therapeutic dose, usually 0.5 to 2 mg daily, is one that reduces the frequency and intensity of episodic attacks, which seldom achieves correction of the biochemical complement abnormalities, and therefore it is not necessary to correct the biochemical abnormality completely. In fact, attempting to do so by increasing the stanozolol dose may be associated with significant hepatic dysfunction.⁸⁻¹⁰ Although stanozolol is no longer marketed, it is generally easily obtainable through a compounding pharmacy.

Adverse side effects of these drugs are a concern. Hepatic toxicity with the use of anabolic steroids with an impeded androgenic effect is well established.^{7,11} Peliosis hepatitis is a life-threatening experience caused by the abuse of such drug therapy.¹⁴ In a detailed study in which liver status was evaluated by hepatic enzyme determination as well as by technetium scanning and percutaneous liver biopsy, the use of anabolic steroids in the treatment of HAE did not cause hepatotoxicity.⁸ At the minimal effective dosage of 0.5 to 2 mg stanozolol daily, the mean maximum values for liver function were within the normal range. Consistent with our experience, the values for hepatic transaminases were elevated when higher daily dosages were administered for attacks or preoperative prophylaxis. Data from the current study suggest that this dose (0.5-2 mg daily) is associated with minimal adverse drug effects in both the short-term and the long-term. When biochemical clinical abnormalities occurred, there was reversal with the reduction of stanozolol dosage without persistent or long-term abnormalities. We were aggressive in minimizing the stanozolol dosage by tapering according to our protocol, and we acknowledge that danazol therapy frequently causes some side effects, such as menstrual irregularities in women with HAE.¹⁵

Since 1966, 42 patients at the Brigham and Women's Hospital have been administered steroids with impeded androgenic effect (17- α alkylated anabolic agents). Four received methyltestosterone and subsequently received,

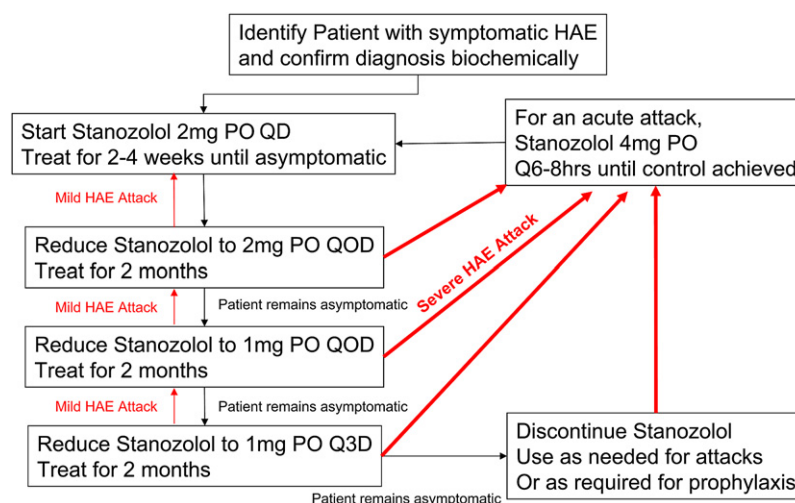


FIG 1. Stanazolol tapering protocol. The flowchart details the scheme by which the dosage of stanazolol was adjusted after the initiation of treatment and the control of symptoms. Patients who remained attack-free were followed closely and the dosage of stanazolol decreased as indicated (*thin black arrows*). If at any time a patient experienced a severe, acute HAE attack, the attack was treated with fresh frozen plasma and the stanazolol was increased to 4 mg by mouth every 6-8 hours (*bold red arrows*) until resolution of the attack. Thereafter, the tapering protocol was restarted. Milder attacks were managed with temporary increases in the dose (*thin red arrows*), and resumption of tapering after control was re-established. QD, daily; Q, every; PO, by mouth; QOD, every other day; Q3D, every 3rd day.

with 33 other patients, oxymetholone. All have subsequently been administered stanazolol over a period of nearly 40 years for long-term chronic prophylaxis. Over this period, we have made 2 important clinical observations about the use of stanazolol in addition to its efficacy and safety. First, most patients can achieve symptomatic control and decrease the dose of stanazolol according to our weaning protocol, increasing and decreasing the dose as circumstances dictate. Second, as the frequency of attacks decreases, most patients with HAE effectively autoregulate, adjusting the dosage of stanazolol themselves.

Nevertheless, long-term monitoring of such patients is essential. At a minimum, patients should be clinically evaluated every 6 to 12 months, including age-appropriate cancer screening. In addition, blood studies (lipid profile, PSA for men, and hepatic transaminases) should be performed, and patients who continue taking stanazolol should have an annual ultrasound.

This drug ensures that patients with HAE a convenient, safe mechanism for self-administration of drug therapy to control their disease. In some instances, patients are able to wean themselves from chronic anabolic steroid therapy.

In conclusion, stanazolol is a safe and an effective drug for the chronic, long-term treatment of patients with HAE, provided such affected patients are closely supervised with routine clinical, biochemical, and radiographic assessment.

We acknowledge with gratitude the advice and suggestions regarding this study and manuscript from K. Frank Austen, MD.

REFERENCES

- Spaulding W. Methyltestosterone therapy for hereditary episodic edema (hereditary angioneurotic edema). *Ann Intern Med* 1960;53:139-45.

- Sheffer AL, Fearon DT, Austen KF. Methyltestosterone therapy in hereditary angioedema. *Ann Intern Med* 1977;86:306-8.
- Gelfand JA, Sherins RJ, Alling DW, Frank MM. Treatment of hereditary angioedema with danazol: reversal of clinical and biochemical abnormalities. *N Engl J Med* 1976;295:1444-8.
- Sheffer AL, Fearon DT, Austen KF. Clinical and biochemical effects of impeded androgen (oxymetholone) therapy of hereditary angioedema. *J Allergy Clin Immunol* 1979;64:275-80.
- Agostoni A, Cicardi M, Martignoni GC, Bergamaschini L, Marasini B. Danazol and stanazolol in long-term prophylactic treatment of hereditary angioedema. *J Allergy Clin Immunol* 1980;65:75-9.
- Farrell GC, Joshua DE, Uren RF, Baird PJ, Perkins KW, Kronenberg H. Androgen-induced hepatoma. *Lancet* 1975;1:430-2.
- Johnson FL, Lerner KG, Siegel M, Feagler JR, Majerus PW, Hartmann JR, et al. Association of androgenic-anabolic steroid therapy with development of hepatocellular carcinoma. *Lancet* 1972;2:1273-6.
- Cicardi M, Castelli R, Zingale LC, Agostoni A. Side effects of long-term prophylaxis with attenuated androgens in hereditary angioedema: comparison of treated and untreated patients. *J Allergy Clin Immunol* 1997;99:194-6.
- Sheffer AL, Fearon DT, Austen KF. Clinical and biochemical effects of stanazolol therapy for hereditary angioedema. *J Allergy Clin Immunol* 1981;68:181-7.
- Sheffer AL, Fearon DT, Austen KF. Hereditary angioedema: a decade of management with stanazolol. *J Allergy Clin Immunol* 1987;80:855-60.
- Bork K, Pitton M, Harten P, Koch P. Hepatocellular adenomas in patients taking danazol for hereditary angio-oedema. *Lancet* 1999;353:1066-7.
- Bowen T, Cicardi M, Farkas H, Bork K, Kreuz W, Zingale L, et al. Canadian 2003 international consensus algorithm for the diagnosis, therapy, and management of hereditary angioedema. *J Allergy Clin Immunol* 2004;114:629-37.
- Prematta M, Gibbs JG, Pratt EL, Stoughton TR, Craig TJ. Fresh frozen plasma for the treatment of hereditary angioedema. *Ann Allergy Asthma Immunol* 2007;98:383-8.
- Cicardi M, Bergamaschini L, Tucci A, Agostoni A, Tornaghi G, Coggi G, et al. Morphologic evaluation of the liver in hereditary angioedema patients on long-term treatment with androgen derivatives. *J Allergy Clin Immunol* 1983;72:294-8.
- Zurlo JJ, Frank MM. The long-term safety of danazol in women with hereditary angioedema. *Fertil Steril* 1990;54:64-72.