ORIGINAL ARTICLE

Treatment of hereditary angioneurotic oedema (HANE) with tibolone

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Summary

Objective Eight women, aged 25–58 years, with hereditary angioneurotic oedema (HANE) were treated with tibolone, a synthetic steroid exhibiting oestrogenic, androgenic and progestational activity.

Design Pilot study.

Results Tibolone at a dose of 2·5–7·5 mg/day significantly reduced the number and severity of attacks and the number of ampoules of C1-esterase inhibitor (C1-INH) needed for symptomatic therapy. The efficacy of tibolone was comparable to that of danazol, while the androgenic side-effects were considerably reduced.

Conclusions Tibolone may represent an alternative to danazol administration for the prophylaxis of HANE in women.

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Introduction

Hereditary angioneurotic oedema (HANE; 106100) is a rare, autosomal dominant inherited disorder caused by either the deficiency (HANE type I) or the lack of function (HANE type II) of C1-esterase inhibitor (C1-INH), which is produced in the liver and inhibits the activation of the first component of the complement cascade. Additional plasma quinines are inhibitory mediators in the fibrinolytic system. Clinically, the disorder is characterized by recurrent attacks of localized subcutaneous or submucous oedema that may develop spontaneously within minutes, after minimal trauma, mental stress, physiological fluctuations of sex hormone levels, various medications or infections. Its resolution can last several days. Submucous oedema can be life-threatening when localized at the upper airways.[1–9]

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HANE was recognized as a disease entity more than 100 years ago by Quincke and Osler. Before prophylaxis and substitution therapy became available, approximately 25% of the affected individuals died because of laryngeal oedema. The sudden death of a young family member was frequently the first indication for HANE and led eventually to diagnosis.

HANE appears, at least in part, to be hormonally dependent, with women generally having a more severe course of the disease than men.[2,10,11] Production of C1-INH by hepatocytes is reported to be stimulated by androgens and inhibited by oestrogens.[4,12,13] Treatment with attenuated androgens such as stanozolol (Stanol®) and danazol (Winobanin®), a derivative of 17-α-ethinyltestosterone with androgenic, anabolic and anti-gonadotrophic properties, has therefore been introduced for prophylaxis.[14–22] For treatment of manifest oedema, substitution with extracts of human plasma containing high concentrations of C1-INH (Berinert®) is used.[4,23–27] Although these therapies are effective in treatment and prevention of attacks, they have severe limitations. Therapy with C1-INH concentrate is expensive and carries a small, but significant, risk of hepatitis transmission and antibody induction has not been observed, but cannot be excluded. The duration of its effect is limited by the clearance of the protein. Danazol can cause androgenization and virilization when administered to women at the recommended doses of 600 mg/day for a prolonged period of time. This may result in irreversible clitoromegaly, deepening of the voice, increase in muscle mass, masculinization of body contours, hirsutism and acne, in addition to adverse metabolic effects on lipoproteins and correlation to hepatocellular focal nodular hyperplasia.[28,29–33]

Tibolone [(7α,17α)-17-hydroxy-7-methyl-19-norpregn-5(10)en-20yn-3-one] is a synthetic steroid with oestrogenic, androgenic and progestogenic properties used primarily for the treatment of menopausal symptoms.[34–36] It is metabolized in the target tissues to the 3α-hydroxy and 3β-hydroxy metabolites and to the Δ4-isomer. The 3α- and 3β-metabolites and tibolone have oestrogenic properties, while the Δ4-isomer, produced in the liver and endometrium, and the parent compound exhibit primarily androgenic and progestational properties.[35–40] As hepatic synthesis of C1-INH is reportedly induced by androgens and as the effectiveness of danazol seems to reside with

Table 1. Characteristics of patients with HANE and dose of tibolone administered per day. Patients 1–3 are from one family, and 4–6 from a second family

Patient no.	Age (years)	Time since diagnosis (years)	Dose of tibolone administered (mg/day)
1	24	12	5
2	57	20	7·5
3	30	16	2·5
4	32	16	5
5	34	16	2·5
6	56	22	5
7	21	9	5
8	25	3	2·5

its androgen activity, we examined whether tibolone, because of its androgenic action, is also effective in the prophylaxis of HANE.

Patients and methods

Eight women (aged 25–58 years; two patients postmenopausal) with HANE were studied after informed consent was obtained. Patients 1–3 belonged to one family, patients 4–6 to a second family. Diagnosis of HANE was based upon clinical symptoms and the findings of undetectable or very low C1-INH concentrations and enzyme activity in plasma (normal values 5–35 mg/dl and > 68%, respectively). Serum C4 level was reduced in all patients (10·7–15·9 mg/dl *vs.* normal value of 20–50 mg/dI). HANE had been diagnosed at least 2 years earlier. Danazol therapy was discontinued for at least 3 months before tibolone administration and after obtaining written consent and local ethical committee approval. During this time, symptomatic therapy was performed by administration of Berinert® whenever necessary. Berinert® is a concentrate of human plasma containing 50 U C1-INH/ml; one ampoule contains 500 U of C1-INH (Aventis Behring, Marburg, Germany).

Tibolone (Liviella®, Organon-Nourypharma, Oberschleißheim, Germany) was administered continuously at an initial dose of 2·5 mg/day. The dose was increased stepwise at 3–6-week intervals up to 7·5 mg/day if necessary. The patients kept a symptom diary and recorded the frequency, severity and localization of oedema as well as signs of androgenization. Clinical signs of androgenization were assessed by the Ferriman and Gallwey score for hirsutism. Ultrasound scanning of the pelvis and breasts of the patients was performed routinely at regular intervals. Blood samples were taken during the control period, 10–14 weeks after the start of tibolone administration and at various intervals (14–30 weeks) thereafter. C1-INH concentrations and function, high density lipoprotein (HDL)- and low density lipoprotein (LDL)-cholesterol, triglycerides and LH, FSH, testosterone, SHBG and dehydroepiandrosterone sulfate (DHEAS) were determined in serum or plasma with specific assays (DPC Biermann, Bad Nauheim, Germany). The frequency of the occurrence of oedema was calculated for a 3-month period before tibolone treatment (control) and for a 3-month period during tibolone treatment. In addition, the severity of oedema was classified as mild, moderate or severe by the patients. The number of ampoules
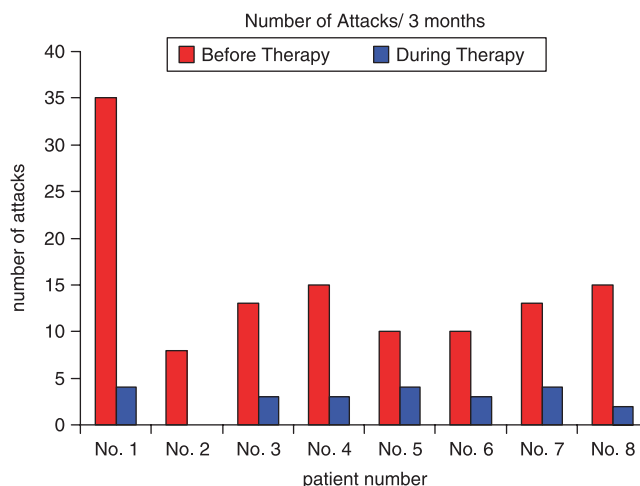

Fig. 1 Number of attacks before and during therapy.

Table 2. Number of attacks during a 3-month control period and during 3 months of treatment with tibolone. Attacks were classified by the patients as mild, moderate or severe. The percentages give the overall decrease of attacks, the sum of the control period is set at 100%

Patient no.	Before treatment			During treatment			% Decrease
	Mild	Moderate	Severe	Mild	Moderate	Severe	
1	25	5	5	2	2	0	89
2	4	2	2	0	0	0	100
3	5	4	4	2	1	0	77
4	6	4	5	1	2	0	80
5	3	3	4	2	1	1	60
6	2	4	4	2	1	0	70
7	4	5	4	2	1	1	70
8	5	5	5	2	0	0	87

of C1-INH that had to be administered was recorded for the 3-month control period and for 3 months during treatment. Treatment has now been administered for 2–4 years; two patients discontinued treatment after more than 6 months because they were planning a pregnancy.

The statistical analysis for determination the significance of differences was made by using the paired Student's *t*-test.
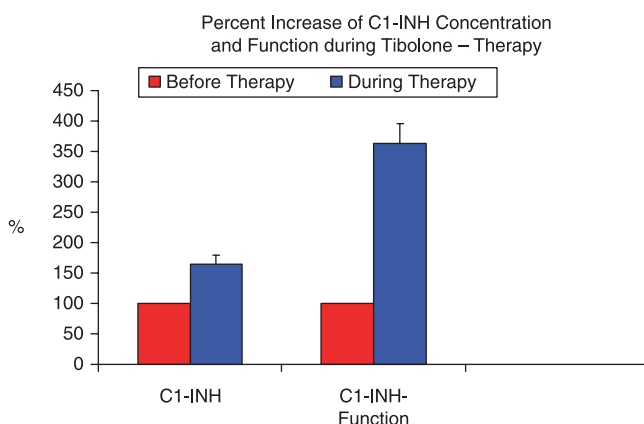
Results

Characteristics, age of the patients, time since diagnosis and the dose of tibolone administered per day are shown on Table 1. In most patients, HANE was diagnosed before or at puberty, with the exception of patient 8, in whom HANE was diagnosed after pregnancy complicated by oedema, which was first mistaken as a symptom of pre-eclampsia.

Most of the patients were treated with 5 mg tibolone daily. The number and severity of attacks before and during treatment are shown in Fig. 1 and Table 2. There was a significant ($P \leq 0.001$)

Table 3. C1-INH concentration and function before and during treatment with tibolone

Patient no.	C1-INH concentration (mg/dl) (normal 5–35 mg/dl)		C1-INH function (%) (normal > 68%)	
	Before treatment	During treatment	Before treatment	During treatment
1	< 5	6·7	14·5	51·5
2	< 5	7·25	12·6	50·4
3	< 5	6·0	15·0	68·3
4	< 5	6·25	28·0	140·0
5	< 5	6·25	22·4	39·8
6	< 5	6·4	10·8	44·9
7	< 5	6·9	13·6	34·0
8	< 5	9·0	21·5	72·8

Table 4. Number of ampoules of Berinert® administered by the patients during a 3-month control period and during 3 months of treatment with tibolone. Patient 2 received a Berinert P injection for preoperative prophylaxis

Patient no.	Before tibolone treatment	During tibolone treatment
1	8	1
2	2	1
3	1	0
4	3	0
5	5	1
6	4	0
7	6	0
8	3	1

Fig. 2 C1-esterase inhibitor concentrations and function during 2–3 months of tibolone therapy. Baseline values before therapy were defined as 100%. The increases in concentration (164%) and function (263%) were significant ($P < 0.05$ and < 0.001, respectively).

decline in frequency and severity of attacks during treatment with tibolone in all patients. Severe symptoms were observed in two of the eight patients only during treatment. The decline in the total number of attacks in each patient (sum of mild, moderate and severe attacks) is shown as a percentage in the far-right column of Table 2. There was a 60–100% reduction in the overall number of attacks during tibolone treatment. Most of the oedema was localized on the extremities; the localization was not influenced by tibolone treatment. Concentrations and function of C1-INH before and during treatment with tibolone are shown in Table 3 and Fig. 2. C1-INH concentrations were below the detection limit of the assay before therapy. During tibolone treatment, there was a small but significant increase in C1-INH concentration. C1-INH function before therapy was between 10% and 28%; these values all are well below the lower limit of normal of 65%. During therapy, C1-INH function increased significantly ($P < 0.001$), reaching normal values in three of the eight patients. Figure 2 shows the percentage increase, with control values set at 100%. The number of ampoules of Berinert® self-administered by the patients during 3 months before and during therapy with tibolone is shown in Table 4. There was a significant decline in the number of ampoules used during tibolone therapy ($P < 0.001$). Levels of HDL- and LDL-cholesterol and triglycerides before and during treatment are shown in Table 5. There was a minimal decline in HDL-cholesterol ($P > 0.05$) as described in earlier studies in post-menopausal women, and essentially no change in LDL-cholesterol ($P > 0.05$). However, triglyceride concentrations were significantly lower during therapy than during the control period ($P < 0.001$). The concentrations of LH, FSH and oestrogen were suppressed during therapy, and there was no increase in progesterone. Testosterone concentrations remained essentially unchanged (< 0.4 ng/ml), while SHBG concentrations declined (data not shown).

Clinical signs of androgenization (hirsutism, acne) did not appear during treatment and did not progress in those patients who exhibited such signs as a consequence of the antecedent therapy with danazol. The effects of treatment on the severity and frequency of the attacks as well as on the concentration and function of C1-INH were sustained for the whole treatment period.

Discussion

HANE has been subdivided into type I and type II disease. Type I disease is caused by the diminished production of a structurally normal C1-INH, while type II is caused by the normal or increased production of a defective protein. According to the results of the C1-inhibitor determination, all of the patients had HANE type I, which was found in 85% of the patients with HANE.[41,42] The results of this pilot study clearly demonstrate that during tibolone therapy in such women, C1-INH concentration and function increase compared to controls.

The clinical significance of this increase is reflected by a reduction in frequency and severity of attacks of angioneurotic oedema. As a consequence there was a considerable reduction in the number of ampoules of Berinert® that were self-administered by the patients. As far as a direct comparison of the effects of danazol and tibolone was possible, the effectiveness of tibolone was not different from that of danazol. The androgenic side-effects of treatment, however, were much less pronounced with tibolone than with danazol. Acceptability and compliance is a very important aspect of therapy, as HANE is an inherited disorder that requires lifelong prophylactic treatment.

Table 5. Concentrations of HDL- and LDL-cholesterol and triglycerides before and during tibolone treatment

Patient no.	Before treatment			During treatment		
	HDL-cholesterol (mg/dl)	LDL-cholesterol (mg/dl)	Triglycerides (mg/dl)	HDL-cholesterol (mg/dl)	LDL-cholesterol (mg/dl)	Triglycerides (mg/dl)
1	60	145	105	41	150	55
2	65	140	125	38	205	65
3	70	135	99	65	145	70
4	75	120	98	55	125	65
5	60	155	110	55	150	49
6	55	170	115	50	168	55
7	59	152	101	60	160	52
8	68	140	103	58	145	64

Most of the deaths that still occur in patients with HANE occur while patients are off medication. The most dramatic effect on laboratory parameters observed during tibolone therapy was the increase in C1-INH function, while the increase in concentration was less pronounced. It is not known whether the increase in function should be attributed to the small increase in concentration or to some other unknown mechanisms. However, similar data have been reported for danazol; it has also been pointed out that serum levels of C1-INH can change considerably and that the most reliable indicator of treatment effects in HANE is the reduction in number and severity of attacks.[18,29] Attacks of HANE may be precipitated by menstruation and oestrogens are reported to have a detrimental effect on the severity of the disorder.[2] Tibolone will suppress endogenous oestrogen secretion and follicular maturation by suppression of LH and FSH secretion and has a protective influence for potential osteoporosis that may contribute to its therapeutic efficiency.[43]

HANE is a rare, chronic, life-threatening disorder, affecting approximately 400 people in Germany. Although effective drugs are available for therapy and prevention, the side-effects of these compounds, especially in women, can be severe and certainly diminish compliance. Tibolone may therefore represent a therapeutic alternative to danazol. Further data need to be collected by controlled clinical observations. Additional studies should also be performed to examine the effectiveness of tibolone in other conditions such as cyclic or idiopathic thrombocytopenia, in which danazol has been shown to be effective, and to examine whether tibolone may safely be administered during parturition to diminish the risk of attacks occurring at this time. The present study was a pilot study. It was not performed blinded and randomized. However, the effects of tibolone treatment observed were dramatic and statistically highly significant. In addition, each patient served as her own control, which may add additional weight to the results and may strengthen the conclusions, partly offsetting the low numbers of subjects.

Conclusions

Tibolone at a dosage of 2·5–7·5 mg/day effectively reduced the occurrence of mild, moderate and severe oedema in patients with HANE. In those patients previously treated with danazol, tibolone was as effective but with less androgenic side-effects. Tibolone therapy was associated with a significant reduction in use of Berinert®, a C1-INH preparation from human plasma. The effectiveness of tibolone was assessed during a 3-month period. All patients were treated for much longer periods of time without apparent loss of effectiveness.

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