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CURRENT METHODS OF TREATING HIRSUTISM: REVIEW AND A 3-MONTH PILOT STUDY WITH TOPICAL ANTIANDROGEN FLURIDIL

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A b s t r a c t

Hirsutism (H) is defined as an excessive male-pattern hair growth in women. H is caused by androgen excess or hypersensitivity of the hair follicles to androgens. The condition is characterised either by no elevation in serum androgen levels and no other clinical features (idiopathic hirsutism) or by an identifiable endocrine imbalance most commonly accompanied by the polycystic ovarian syndrome.

Systemic therapy for this condition always requires one or more years' treatment for maximal benefit and long-term approaches are usually necessary as recurrence is frequent. Systemic therapy includes estrogens, antiandrogens, finasteride, corticosteroids, gonadotropin-releasing hormone agonists or insulin-sensitising agents.

Local therapy includes plucking, bleaching, depilatory creams and waxes, electrolysis, electrocoagulation, and laser removal. Another possibility is eflornithine hydrochloride cream which directly affects the cell cycle in the pilosebaceous unit.

The authors present the results of a 3-month pilot study in female hirsute patients with a topical non-systemically resorbable antiandrogen fluridil 2 % formulated in isopropanol and a carbox gel. The purpose of the study was to evaluate the efficacy and safety of a new 2% fluridil gel in the treatment of hirsutism. The sample included a total of 10 female subjects aged 25 to 68 years (mean age 48.1) with manifestations of facial hirsutism. The patients applied fluridil once a day for 3 months and manifestations of hirsutism were recorded on digital camera at the outset and at the end of the study. The efficacy and safety of the preparation were evaluated by the subjects themselves and the physician after three months of application.

Nine patients showed improvements in terms of reduced rate of hair growth and thinning of individual hairs in the treated area. Tolerance was evaluated as excellent by all 10 subjects and by physicians, no undesirable effects occurred during the application.

K e y w o r d s

Hirsutism, Antiandrogens, Fluridil

INTRODUCTION

Hirsutism is typically defined as an excessive male-pattern hair growth in women. It is distinguished from hypertrichosis, a term used to describe the androgen-independent growth of body hair which is vellus and prominent in nonsexual areas (*1*). Most hirsutism is androgen-dependent and associated with androgen excess although this concept may be too simplistic to explain pathological states of the pilosebaceous unit (PSU) such as hirsutism, acne, seborrhoea, and androgenetic alopecia (*2*). Hirsutism is part of the hyperandrogenic skin syndrome; androgen-dependent midline hair grows primarily on the upper lip, chin, cheeks, intermammary area, inner thighs, lower back, and intergluteal area. The most common cause of androgen-dependent hirsutism is the polycystic ovary syndrome (PCOS). Other possible aetiologies are an androgen-secreting tumour, Cushing's syndrome, non-classical congenital adrenal hyperplasia (NC-CAH), and exogenous androgens due to anabolic steroid use or androgen overdose in postmenopausal patients. The term "idiopathic hirsutism" is often used to describe hirsutism in women with normal circulating androgen levels, but this may reflect the limited ability to assess androgen activity in the peripheral compartment (*2*).

Although treatments can improve hirsutism, most medical therapies do not produce a significant reduction in hair growth that most women desire, and treatments are often more palliative than curative. In obese women, weight loss as a therapy should be emphasised, regardless of the aetiology of the hirsutism. Upper body obesity has been shown to be associated with a reduced sex hormone-binding globulin level and increased free testosterone levels in both non-hirsute and hirsute women. Both contribute to hyperandrogenism (3).

Treatment of hirsutism includes cosmetic measures, systemic pharmacological therapy, and novel pharmacological agents for topical use. Mechanical hair removal like shaving, plucking, waxing, depilatory creams, electrolysis, and laser vaporisation can control hirsutism, and these are front-line treatments for most women. Shaving may be the most common temporary method. Judicious plucking can also be helpful if tolerated, but care must be taken to avoid folliculitis, pigmentation, and scarring. Waxing and depilatories are used less commonly, because of their potential adverse side effects such as skin burning or rash (*4*). Electrical epilation by high-frequency short-wave diathermy or galvanic electrolysis offer permanent methods of hair removal. Laser therapy and light-assisted hair removal are based on the principle of selective photothermolysis (*5*). Ruby, alexandrite, diode, and neodymium:yttrium-aluminum-garnet (Nd:YAG) lasers, and a broad-band intense pulsed light have been used. Due to the presence of hair follicles in various stages of the hair growth cycle, multiple extended treatments may be necessary.

Systemic pharmacological therapy of hirsutism always requires a year or more and long-term applications are usually necessary as recurrence is frequent. All currently available medical treatments for hirsutism are antiandrogens. These can act at

various levels, including the hypothalamus, pituitary gland, adrenal glands, gonads, and target cells in the skin. Systemic androgen receptor blockers, which comprise the antiandrogens used most often in dermatology, include cyproterone acetate, spironolactone, and flutamide (*3*). Other valuable drugs that reduce androgen expression include oral contraceptives, 5α-reductase inhibitor, finasteride, analogs gonadotropin-releasing hormone (Gn-RH), and insulin-sensitising agents.

Oral contraceptives, although not specifically antiandrogens, are commonly used in women with androgen-mediated hirsutism. These reduce ovarian hormone production and secretion, which results in an overall reduction in androgen secretion. They also minimalise antiandrogen side effects through cycle regulation (*3*).

The cyproterone acetate formulation oral contraceptive (Diane-35®, Minerva®), is felt to be effective in treating hirsutism. Cyproterone acetate is an androgen receptor blocker and potent progestin. It also has an antigonadotropic effect. It has been in common use for over 30 years and is currently employed widely as an antiandrogen, as the progestin component of an oral contraceptive, and in some regimes of hormone-replacement therapy (*6*). Other formulations containing the progestogens with antiandrogen activity are drospirenon (Yadine®), dienogest (Jeanine®) or chlormadinonacetate (Belara®). These are especially useful in hirsute women who also require contraception. Individual patient response and tolerance often determine which combination is used. The lower dose pills containing 30–35 μg oestrogen (usually ethinylestradiol) are favoured because they have been established as having minimal cardiovascular complications (*7*). Oral contraceptives may be seen as first-line treatment for hirsutism, particularly in those women desiring contraception. Long-term safety profiles allow for prolonged therapy if needed. They can be used alone or in combination with specific antiandrogens (*3*).

Spironolactone is a synthetic steroid structurally related to aldosterone that acts by competitively blocking cytoplasmic receptors for dihydrotestosterone. It was previously thought to increase the metabolism of circulating androgens by increasing the activity of cytochrome P450 enzyme but this action seems to have little effect on hormone levels (*8, 9*). Spironolactone is primarily used as a diuretic and antihypertensive because it is a specific antagonist of aldosterone. Several studies have demonstrated the efficacy of spironolactone in the treatment of hirsutism (*10, 11, 12*). It has also been found to be of benefit in androgenetic alopecia, which often coexists with hirsutism (*13*). Doses of spironolactone range from 50 to 300 mg/day. Side effects are dose-related and include menstrual irregularities, including post-menopausal bleeding, breast tenderness or enlargement, and fatigue. Spironolactone crosses the placenta and has the potential to emasculate a male foetus. Combination with oral contraceptives is useful and minimalises the hormonal side effects (*7*). The anti-aldosterone effect can result in measurable increase in serum potassium, so advice should be given to patients to avoid potassium-rich diets, including salt substitutes, and care should be exercised with concurrent use of other potassium-sparring drugs. Low-dose spironolactone between 50 and 100 mg/day is generally well tolerated (*14*).

Flutamide is a non-steroidal antiandrogen that acts by inhibiting androgen uptake and by inhibiting nuclear binding of androgen within the target tissue (*15, 16*). The main indication is prostate cancer. It has been used to treat hirsutism at a dose of 125–250 mg twice daily with or without the addition of an oral contraceptive (*1*). The most common side effects of flutamide are dry skin, hot flushes, decreased libido, fatigue, and gastric disturbance. Menstrual irregularities are common when flutamide is used without the concomitant use of oral contraceptives (*17*). Hepatotoxicity is the most important side effect and liver function should be monitored regularly for the duration of treatment (*18, 19*).

Finasteride, a 4-aza-steroid, approved for treating benign prostatic hyperplasia, is an inhibitor of type 2 5 α-reductase that converts testosterone to dihydrotestosterone (DHT). Many studies have demonstrated some degree of efficacy of finasteride in treating hirsutism (20). It has been found effective in the treatment of hirsutism at a dose of 5 mg/day (*21*). Finasteride is better tolerated than antiandrogens, with minimal hepatic and renal toxicity, but it has the highest risk of teratogenicity in a male foetus and adequate contraception must be used (*2*).

Glucocorticoid therapy can be helpful in those women with hyperandrogenism from an adrenal source, as adrenal androgens are more sensitive than cortisol to the suppressive effects of glucocorticoids (*22*). The main use of corticosteroids has been to treat hirsutism associated with congenital adrenal hyperplasia (CAH). They have also been used empirically to treat hirsutism associated with polycystic ovarian disease (*23*). Prednisone in doses of 5–10 mg at bedtime is usually effective in suppressing adrenal androgens while posing minimal risk of glucocorticoid excess such as adrenal atrophy, weight gain, and decreased bone mineral density (*1*).

Gonadotropin-releasing hormone (GnRH) agonists are decapeptides resembling native GnRH. Chronic administration of GnRH agonists suppresses pituitary-ovarian function, thus inhibiting both ovarian androgen and oestrogen secretion. These agonists have been reported to be effective in the treatment of hirsutism (*24*), namely leuprolide acetate and buserelin. Owing to the concomitant reduction of serum oestrogen levels and reductions in bone mineral density observed when GnRH agonists are used alone (*25*), it is unwise to use these agents for longer than 6 months. GnRH agonists are relatively expensive and are not considered first-line therapy. They should only be used for particularly severe hirsutism or hirsutism that has not responded to other forms of treatment.

Insulin-sensitising agents, on the other hand, have been adapted from the treatment of type-2 diabetes and they improve ambient hyperinsulinemia by increasing insulin sensitivity. Hyperinsulinemia may play a critical role in the pathogenesis of the hyperandrogenism of PCOS, the most common cause of female hyperandrogenism (*1*). Given the prolonged onset of action for reducing hirsutism, longer periods of observation are needed. In the largest and longest randomised trial to date of these agents, troglitazone at the highest dose of 600 mg/day was found to significantly improve hirsutism in women with PCOS (*26*). In several studies with

metformin, hirsutism was improved slightly (*27*). Further study is needed to detect differences between classes of insulin-sensitising agents and establish prolonged benefit over a longer duration of study.

Eflornithine hydrochloride cream (Vaniqa®) is useful for topical treatment of hirsutism. The cream is the only agent that directly affects the cell cycle in the pilosebaceous unit (PSU). This is a potent, irreversible inhibitor of the enzyme ornithine decarboxylase, which is necessary for production of the polyamines that mediate cell migration, proliferation, and differentiation. Binding of DHT to the androgen receptor is associated with stimulation of ornithine decarboxylase synthesis and proliferation of hair matrix cells (*28*). Inhibition of this enzyme limits cell division and function. This agent is generally well tolerated. The most common side effects are stinging and skin rash (*29*).

Fluridil (2-hydroxy-2-methyl-N-[4-nitro-3-(trifluoromethyl)phenyl]-3-(2,2,2-trifluoroacetylamino)propanamide) was developed as a topical antiandrogen suitable for hyperandrogenic skin syndromes. Topical antiandrogen fluridil suppresses the cutaneous androgen receptor, is hydrolytically degradable into fragments devoid of antiandrogenic activity (*Fig. 1*), is non-irritating and systemically non-resorbable. At a 5 ng/ml detection limit, no fluridil or catabolites were found in human serum. In a clinical study conducted at our facility, fluridil in solution (Eucapil®, Interpharma Praha, Czech Republic) has been shown to be effective and safe in the treatment of men with androgenetic alopecia (*30, 31*). Based on these results we conducted an orientational three-month pilot study to evaluate the efficacy and safety of 2% fluridil gel in female patients with face idiopathic hirsutism.

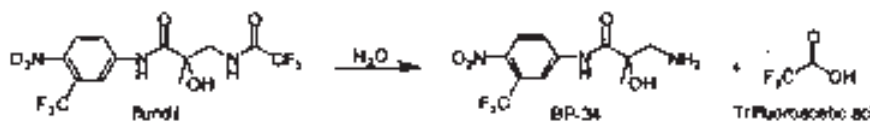

Fig. 1
Hydrolytic decomposition of fluridil

MATERIAL AND METHODS

The study substance was a 2% fluridil gel containing 2% fluridil, 5% carbopol ETD 2050, and 93 % of isopropyl alcohol (Interpharma Praha, Czech Republic).

The patient sample included a total of 10 females, aged 25 to 68 years with face hirsutism. They were selected from the outpatient database at the Department of Dermatology, University Hospital Olomouc. Photographic documentation was obtained on the day of inclusion in the study using a digital camera, Camedia 2000, Olympus. A total of 3 baseline photographs of the affected area was taken for each study subject (front view, and right and left profile views). In the same way, photographs were taken at the time of study termination (i.e. after 3 months of application of the fluridil gel).

At visit 1, blood samples were obtained for laboratory tests of serum levels of total testosterone and sex hormone-binding globulin (SHBG). The subjects then received the study substance to be used for three months (100 g of fluridil gel), and they received instructions for proper application. The gel was applied as a thin layer over the affected area (upper lip, chin, and also neck when appropriate) once a day in the evening.

At visit 2, i.e. after three months of application, the efficacy and tolerance of the preparation were assessed, and another blood sample and urine sample were obtained to detect possibly occurring accumulation of fluridil. A second series of photographs of the affected area was obtained and the study was terminated.

RESULTS

1. Evaluation of efficacy of 2% fluridil gel

Evaluation by subjects:

Nine out of ten subjects observed a favourable effect of fluridil on appearance of hirsutism, in terms of reduced rate of hair growth (7 subjects) and thinning of the hairs (9 subjects).

Evaluation by physician:

Comparison of the photographs taken before fluridil use and those obtained after the termination of use *(Figs. 2, 3)* showed improvements in terms of reduced hair in 9 subjects.

2. Evaluation of tolerance of 2% fluridil gel

None of the 10 subjects reported undesirable effects over the course of treatment in the sense of skin irritation, burning sensation, etc. Two subjects judged the odour of the isopropanol gel unpleasant and too intense immediately after the application.

DISCUSSION

Some women with hirsutism may be found to have hyperandrogenemia or reduced androgen binding to plasmatic proteins, while these levels may be physiological in others. In the latter, the cause of increased hair growth is greater sensitivity of target tissues, i.e. hair follicles, to androgens. This, in turn, may depend on exaggerated 5α-reductase activity redirecting testosterone metabolism to its biologically more active metabolite dihydrotestosterone, or it may result from an increased number of androgen receptors in the target tissue cells.

We found in our sample 2 subjects with increased testosterone levels, and 4 with reduced levels of SHBG, and a reduction in SHBG was invariably shown in all subjects with increased testosterone levels *(Table 1)*. No correlation was shown in the sample between increased testosterone levels, or reduced SHBG levels and treatment response. The methods of determination of 5α-reductase level or androgen receptor density in the target tissue are not available at present.

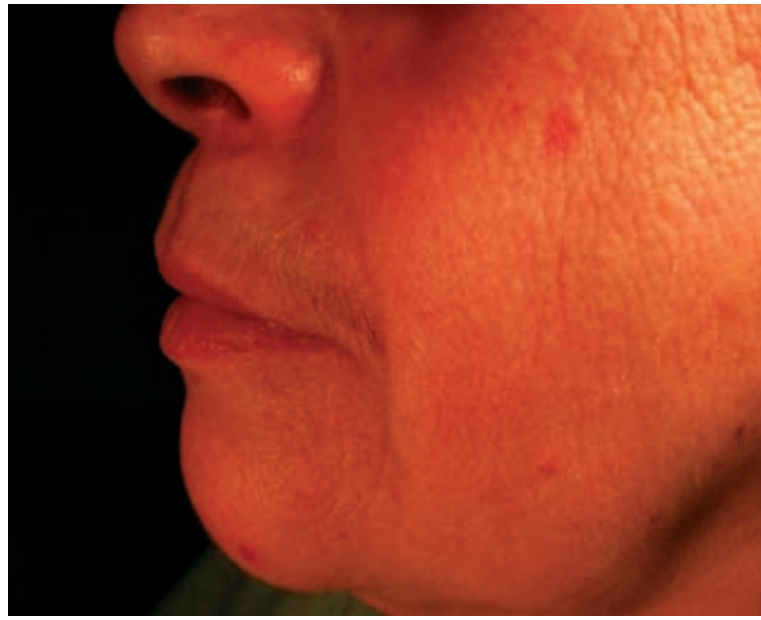

Fig. 2
Patient with facial hirsutism before fluridil treatment

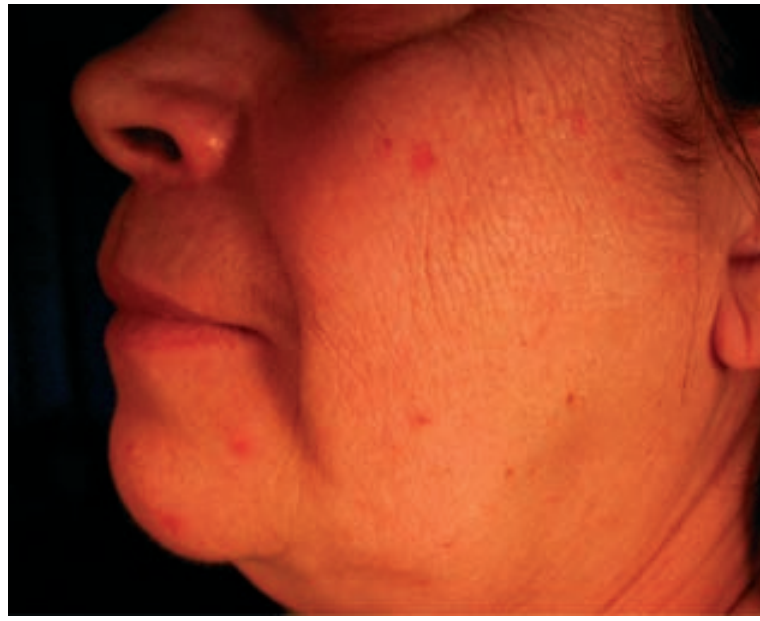

Fig. 3
Patient with facial hirsutism after 3-month fluridil treatment

Evaluation of the preparation's efficacy in the present study was limited however and relied on:

1. subjective observation by patients who focused on changes in the rate of hair growth and hair thickness during the course of fluridil gel application,

2. evaluation of photographs of affected areas before and after treatment by a physician.

Four subjects from the sample had been using tweezers to correct the hairs or were undergoing electrocoagulation epilation before study inclusion. The photographs at the outset and termination of the trials were always taken in the same time interval after epilation to ensure comparability of the photographs.

Table 1
SHBG and testosterone levels in patients with facial hirsutism

Serial number and subject initials	**SHBG level**	**Testosterone level**
	nmol/l	**nmol/l**
1. M.R.	63	0.8
2. A.N.	**29**	1.1
3. V.H.	34	2.3
4. M.M.	**21**	**2.4**
5. P.P.	**15**	**3.2**
6. A.Z.	34	2.2
7. V.M.	**26**	2.0
8. D.R.	46	1.9
9. B.J.	37	0.7
10. M.Š.	**17**	0.5
Normal range for SHBG:	30–100 nmol/l	
Normal range for testosterone:	0.2–2.3 nmol/l	

CONCLUSION

Hirsutism of sufficient severity that medical assistance is sought can have serious social and psychological effects in women. Since hair and masculinity are associated, these women require reassurance that they are not turning into men or are excessively masculine. They will also need advice on cosmetic measures to remove hair. Given the serious psychological problem for most women, alternative approaches to treatment are necessary, especially as current treatment methods are unsatisfactory.

A number of modalities are available. In general, multiagent treatment with a variety of mechanisms has been preferred. In conclusion, all women presenting to a clinician with unwanted hair should be given advice on cosmetic measures including electrolysis and laser therapy. Medical treatments can last several months, with years required to obtain the full benefit. The future promises further developments and utilisation of agents for topical use such as eflornithine or antiandrogen fluridil.

The present clinical study has shown that a 2% fluridil gel is a safe and effective treatment method of hirsutism. However, this preparation is not available yet. Compared to systemic administration of antiandrogens, topical fluridil does not affect general health and sexual functions and, more importantly, does not decrease libido. None of the subjects experienced undesirable effects in the sense of contact or irritation reaction. Fluridil appears to be a suitable alternative to treat topically hirsutism, both in monotherapy and in combination with other treatments.

A c k n o w l e d g e m e n t s

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SOUČASNÉ MOŽNOSTI LÉČBY HIRSUTISMU: PŘEHLED A VÝSLEDKY TŘÍMĚSÍČNÍ PILOTNÍ STUDIE S LOKÁLNÍM ANTIANDROGENEM FLURIDILEM

S o u h r n

Hirsutismus lze definovat jako nadměrný růst terminálního ochlupení u žen v typicky mužských lokalitách. Vzniká v důsledku nadbytku androgenů nebo při zvýšené citlivosti vlasových folikulů k androgenům. Toto onemocnění bývá často sdruženo se syndromem polycystických ovarií. Jako idiopatický hirsutismus je označován zvýšený růst ochlupení u žen v sexuálních lokalitách při normálních sérových hladinách androgenů a je předpokládána zvýšená citlivost androgenních receptorů ve vlasovém folikulu. U systémové terapie je nutné vždy zvážit riziko dlouhodobé aplikace preparátů, které podáváme minimálně rok a více, abychom dosáhli maximálního efektu. Po vysazení terapie dochází často k recidivám potíží.

Systémová léčba hirsutismu zahrnuje estrogeny, antiandrogeny a další látky, jako jsou finasterid, glukokortikoidy, analoga GnRH nebo látky zlepšující senzitivitu na inzulin.

Mezi lokální možnosti léčby hirsutismu patří kosmetické přístupy jako holení, trhání, bělení, depilace krémy a vosky, elektrolýza, elektrokoagulace a laserové ošetření. Novou možností je aplikace eflornitinu ve formě krému, jehož aplikace narušuje buněčný cyklus v pilosebaceózní jednotce.

Autoři prezentují výsledky tříměsíční pilotní studie s lokálním antiandrogenem fluridilem ve 2% koncentraci ve formě gelu u pacientek s hirsutismem v obličeji. Cílem studie bylo ověřit účinnost a snášenlivost 2% fluridilového gelu v léčbě hirsutismu. Studie byla projednána a schválena lokální etickou komisí a před zařazením do studie podepsaly pacientky informovaný souhlas. Do studie bylo zařazeno celkem 10 probandů ženského pohlaví ve věku od 25 do 68 let, s průměrným věkem 48,1 roků s projevy hirsutismu v obličeji. Pacientky aplikovaly testovaný přípravek 1x denně po dobu 3 měsíců. Projevy hirsutismu byly zaznamenány pomocí digitálního fotografování na začátku a na konci studie. Po třech měsících aplikace byla hodnocena účinnost a snášenlivost přípravku pacientkou i lékařem.

U 9 probandek bylo pozorováno zlepšení projevů hirsutismu, které se projevilo zpomalením růstu ochlupení a ztenčením jednotlivých chloupků v ošetřované oblasti. U všech 10 probandek byla snášenlivost hodnocena jako výborná, během aplikace se nevyskytly žádné vedlejší účinky.

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