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CURRENT THERAPIES OF FEMALE ANDROGENETIC ALOPECIA AND USE OF FLURIDIL, A NOVEL TOPICAL ANTIANDROGEN

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A b s t r a c t

Androgenetic alopecia (AGA) is the most common form of alopecia. As an androgen-dependent process, AGA miniaturises the hair follicles in genetically predisposed men and women. Currently, AGA in women is usually treated with topical minoxidil and, unlike in men, by systemic antiandrogens. Hair loss in women is usually less severe than in men; nevertheless, in women AGA causes serious psychological problems. New safe and effective approaches to AGA are desirable. Fluridil was developed as a topical antiandrogen, suitable for the treatment of hyperandrogenic skin syndromes. The cosmetic product Eucapil® containing 2% fluridil in isopropanol was tested in women with AGA in a 9-month open study. A total of 11 females (average age of 35 years) and stage I–II according to Ludwig were enrolled into the study. Hair growth was evaluated using phototrichograms. The anagen/telogen % ratio after 6 and 9 months showed no statistically significant changes ($p<0.05$), but after 9 months there was no AGA progression.

The anagen hair-stem diameter was measured using optical microscopy, which demonstrated a statistically significant increase after 6 months ($p<0.02$) and 9 months ($p<0.001$). No morphological changes using scanning electron microscopy were found. Two patients discontinued the study due to skin irritation at the application site, which we determined to be caused by isopropanol. No changes in biochemical or haematological values were found and the questionnaires suggest that topical Eucapil® lacks systemic effects. Topical Eucapil® is an attractive therapeutic alternative in female AGA because of its safety and efficacy.

K e y w o r d s

Female AGA, Fluridil, Topical antiandrogen, Eucapil®, Hair diameter

INTRODUCTION

Androgenetic alopecia (AGA) is the most common form of alopecia. Caucasian men and women suffer from androgen-dependent hair loss frequently (50 % beyond the age of 40). The first signs of AGA may start after puberty (*1*).

AGA has been reported to be a polygenic trait believed to involve several genes for both sexes. It is an androgen hormone-dependent process with continuous miniaturisation of hair follicles in both genetically predisposed men and women (*2, 3*). Systemically and also in the hair follicle cells, testosterone is converted into the more active androgen dihydrotestosterone (DHT) by 5 α-reductase enzyme. The androgens bind to androgen receptors (AR) in the hair follicle, which triggers a process reducing the anagen phase of the hair cycle. Gradually, over succeeding cycles, the terminal hair converts into a thinner and shorter vellus hair (*4, 5*). The density of the AR in the hair follicles varies according to location, which is genetically determined. Age also plays an important role in AGA (*1*).

The aetiopathogenesis of AGA, referred to as male pattern hair loss (MPHL) in men and female pattern hair loss (FPHL) in women, is not yet fully understood. The androgen dependence of AGA in women is less clear than in men, although until recently it has been generally assumed that both MPHL and FPHL result from an abnormal sensitivity of scalp hair follicles to circulating androgens (*6, 7*). However, clinical trials with finasteride, a type-2 5 α-reductase inhibitor, suggest that the pathophysiology of AGA in women differs from that in men. In contrast to men, finasteride does not stop the hair loss and does not improve hair growth in postmenopausal FPHL women. The absence of any specific clinical or histological findings after finasteride in these patients suggests that the pathogenesis of FPHL in women may be different (*6, 8*). It is always necessary to diagnostically exclude the possibility of endocrine dysfunction.

The diagnosis of AGA is usually made clinically. The finding is typical, especially in patients with a positive family history of gradual hair loss (*1*).

AGA in women is less frequent than in men. It develops most often at the vertex as a diffuse thinning of hair and gradual reduction of hair density. The hair boundary line above the forehead is usually maintained, in contrast to men. The density of hair remains the same in the occipital and parietal areas *(Fig. 1)*. Women go completely bald rarely. Clinical evaluation of AGA in women uses a three-level classification according to *Ludwig* (*9*).

In case of diagnostic doubt, laboratory and histopathological examination of scalp biopsies are useful (*10–13*).

Until recently the absence of a truly effective treatment for AGA led to a general lack of interest in it as a clinical condition. Fortunately, currently drug therapies of proven efficacy are available (*4*).

Minoxidil, a pyrimidine derivative, and its analogues, such as aminexil, are frequently used agents for the topical use. Minoxidil prolongs the anagen phase of the

hair cycle. In the case of AGA, topical application of minoxidil 2% or 5% solution is necessary twice a day over a longer period of time. The claimed mode of action of aminexil as an antifibrotic agent is to inhibit collagen formation around the hair follicle and to maintain the follicle survival. Aminexil's primary claim is prevention of further hair loss (*8*).

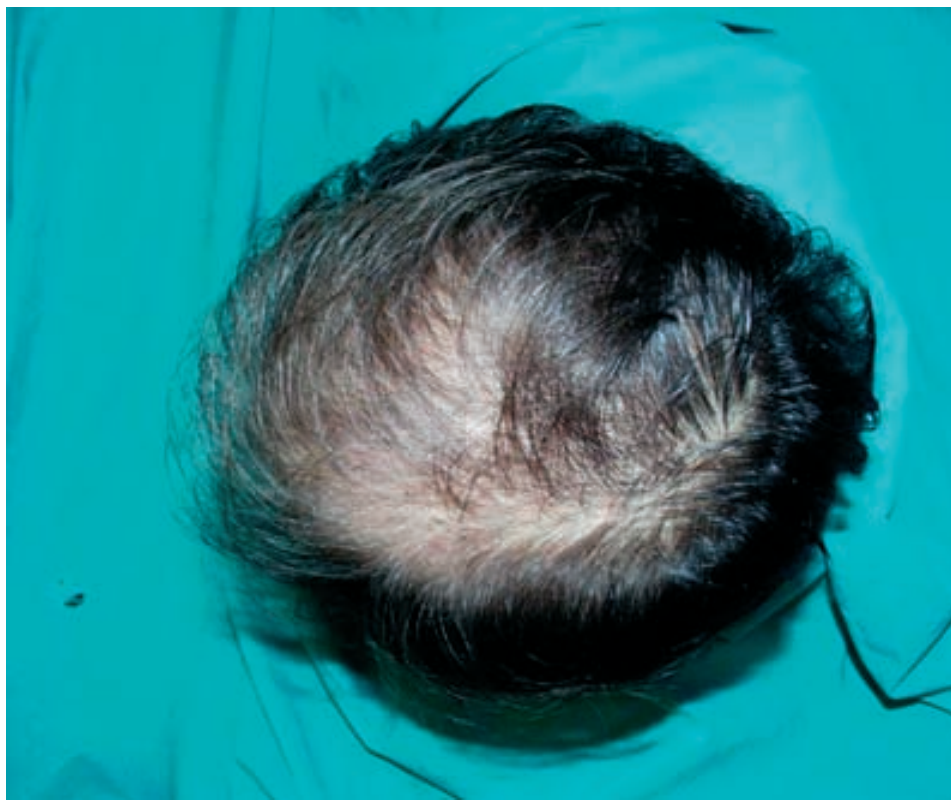

Fig. 1
Clinical findings of female AGA (grade II)

Another agent for FPHL treatment is Anastim®, a combined preparation containing the RTH 16, extracted from Ruscus aculeatus. RTH 16 stimulates the production of VEGF (vascular endothelial growth factor) in the dermal papilla. Other effective components are extracts from Sabal serrulata palm tree (a 5α-reductase blocker) and tocopheryl-nicotinate, which claim to improve blood circulation.

Other products used for external treatment are oestrogen-containing products, which prolong the anagen phase of the hair cycle thus preventing premature hair loss.

Unlike in men systemic antiandrogens administered are frequently used in FPHL. In pregnant women the systemic antiandrogens, by blocking the androgen receptor

(AR), might give rise to ambiguous genitalia of male foetuses, therefore in women with childbearing potential these drugs should be avoided or used in combination with oestrogens for contraception (*1*).

In clinical practice the systemic antiandrogens **cyproterone acetate**, **chlormadinone acetate**, **dienogest**, and **drospirenone** are used in combination with oestrogens ensuring contraception (COC) at the same time. These antiandrogens are also potent progestins. The most potent antiandrogen in this group is cyproterone acetate (CPA), which is widely used in the world with the exception of the USA. It is available for women with childbearing potential in the combined product Diane 35® containing 2 mg cyproterone acetate and 35 μg ethinylestradiol (*14–17*). The effect is rather complex as these drugs act on various levels. The antiandrogen component blocks the DHT binding to the AR in the target tissue, reduces the activity of 5α-reductase, and decreases the production of androgens in the ovaries. The oestrogen component increases the liver production of sex hormone-binding globulin (SHBG), which reduces the levels of free serum testosterone. The minimum dose of the oestrogen component (i.e. ethinylestradiol) stimulating SHBG liver production is 30–35 μg pro pill.

CPA in combination with ethinylestradiol may prevent further progression or reverse to some extent AGA in women. In severe hyperandrogenic conditions where androgenetic hair loss does not stop, CPA (Androcur® 10, 50 mg tablets) can be added up to 50 mg daily for the first 10 (*18*) or 15 days of the cycle (*1*). A combination of 1 mg cyproterone acetate and 2 mg estradiol valerate is Climen®, which is nevertheless intended only for women who lack sufficient oestrogens after natural, precocious, or castration menopause. Unlike Diane 35, Climen is not a contraceptive.

Oestrogen hormones in monotherapy can be used for systemic administration in women, in the form of hormonal replacement therapy, particularly when oestrogen production is reduced, especially during premenopause or menopause. Close cooperation with the gynaecologist is always needed.

Finasteride, an inhibitor of type-2 5 α-reductase, is suitable for systemic treatment in males only.

Drugs containing vitamins, amino acids and trace elements may be used as supportive therapy. Gene therapy may become in the future another possibility for patients with AGA.

Hair loss in women is usually less severe than in men, nevertheless in women AGA causes serious psychological problems. New, easily accessible, safe, and effective approaches to AGA are desirable.

Fluridil was developed as a topical antiandrogen suitable for the treatment of hyperandrogenic skin syndromes. Topical fluridil, owing to its hydrophobicity, dissolves in the sebum and blocks AR in the hair follicles. Fluridil in the aqueous environment rapidly decomposes into fragments which lack hormonal effects *(Fig. 2,3)*, have acceptable systemic tolerance, and are rapidly eliminated. Neither fluridil nor

its decomposition products were detected in the studies involving AGA in humans (*19, 20*). In 40 male AGA patients no detectable quantities of either substance were found by high-performance liquid chromatography (HPLC) beyond the limit of the visual detection of 5 ng/ml in the serum. The 21-day test on 20 volunteers failed to prove any irritation potential (*20*). We report more on this in a 9-month initial study in females with AGA.

MATERIAL AND METHODS

The efficacy and safety of 2% solution of fluridil in anhydrous isopropanol (Eucapil®, Interpharma Praha) was tested in an open clinical study. The study was approved by the local ethics committee in Olomouc.

A total of 11 female patients with AGA, 6 with stage I and 5 with stage II according to Ludwig *(Fig. 3)*, 22 to 45 (average age 35 years), were enrolled. The inclusion criteria were: phototypes II – IV, AGA stages I – II according to Ludwig, administration of Diane 35® at least 3 months prior to the enrolment into the study, no other systemic or topical treatment at least one month prior to enrolment.

Two ml of Eucapil® were gently massaged into the dry scalp once a day in the evening. Given the instability of the active ingredient in an aqueous setting, the participants were required to apply Eucapil® only on dry scalp and also to limit shampoo washes to a maximum of 2 times a week, also at least 12 hours after the last Eucapil® use.

Clinical assessment

The effect on AGA was evaluated by the physician and by the patient using a four-level scale: 0=excellent, 1=good, 2=none, 3=worsening, after 3, 6 and 9 months of fluridil treatment. Tolerance was evaluated in a similar manner: 0=excellent (no adverse effects), 1=good (less recognisable adverse effects, no reason for discontinuation of the therapy), 2=poor (severe adverse effects, justifying the therapy discontinuation). At the end of the study, the efficacy and tolerance of the product throughout the study were evaluated using a point score. This score was calculated as an arithmetic mean of the point scores of all patients (subjectively and by the physician) for the selected time interval.

In the 2 women who discontinued the study due to skin irritation, epicutaneous tests were conducted to exclude or confirm contact allergic reaction to the product. The following samples were used for the tests: fluridil 2% solution in isopropanol, fluridil 0.5% solution in isopropanol (allergological concentration), and pure isopropanol. The reactions were read after 48 hours.

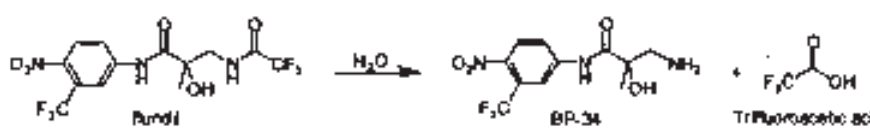

Fig. 2
Fluridil and its hydrolytic decomposition

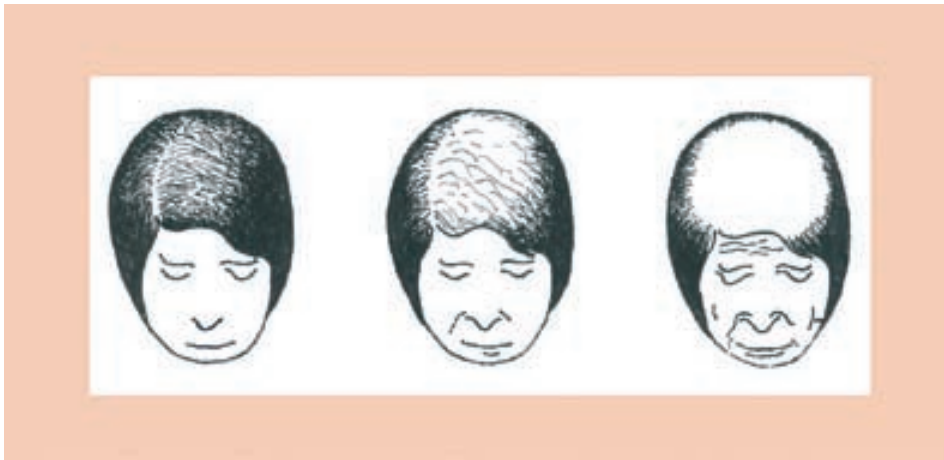

Fig. 3
Ludwig's classification of female AGA (grades I–III)

Phototrichograms

A phototrichogram (PTG) is a non-invasive method (*20, 21*) consisting in photographing the predefined area immediately after shaving the hair, when the hair follicles can be identified as small dots. Seventy-two hours later, the hairs in the growth phase (anagens) appear as linear formations – having a length of approximately 1.2 mm, while the hairs in the resting phase (telogens) do not grow *(Fig. 4)*.

The scalp test area was marked by permanent make-up, i.e. a temporary tattoo, and shaved before the fluridil administration. This site was photographed 72 hours later, through a round plastic template of 1.2 cm in diameter (i.e. 1.1 cm^2) using digital camera (Camedia 2000, Olympus). The images were stored electronically. Subsequently, the hair follicles were counted on the computer monitor, under magnification. Given the individual differences in the total count of hair follicles, the percentage anagen/telogen ratio was used. The phototrichograms were continued after 6 and 9 months and the data statistically processed.

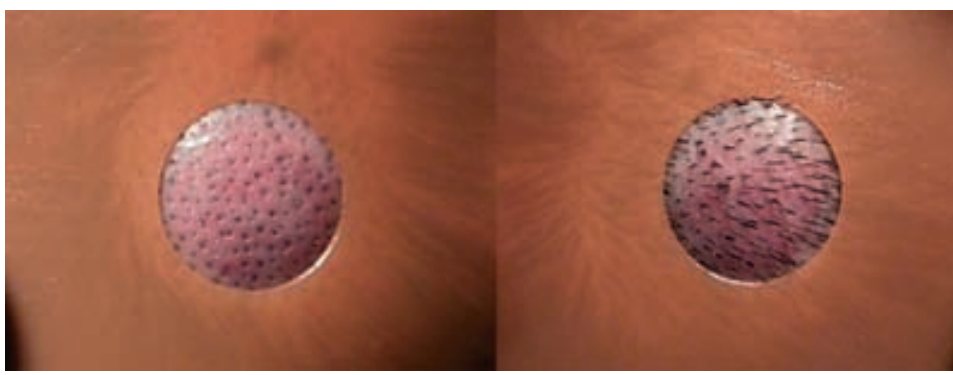

Fig. 4
Phototrichograms
a) immediately after shaving b) after 72 hours

Hair stem diameter

Before the study onset an area in the frontoparietal region of about 1.5 cm in diameter was marked in the margins using permanent make-up. This area was shaved and approximately 50 newly growing hairs (anagens) were collected by cutting closely to the skin three weeks later. The hair diameter was measured by a Carl Zeiss Jenamed microscope with an image analysis device Kontron (Germany), calibrated using a micrometric grid, with a planachromatic 20x objective. Ten diameters were read at a 5 – 10 mm section of the hair stem. A total of 40 hairs were evaluated for each collection, in each individual by a single operator.

Hair surface morphological changes

Scanning electron microscopy (SEM) was used. Five hairs from each patient were glued onto a metal beam using conductive tape, and the hairs were metal-coated using an E 5100 Polaron (Great Britain) coating unit and viewed in the scanning electron microscope Tesla BS 340.

The evaluation of the hair stem diameter and hair surface morphological changes was carried out, similarly to the phototrichograms, at the enrolment into the study and after 6 and 9 months.

Global scalp images

Global scalp images were taken from the above patients upon the enrolment and after 6 and 9 months, and evaluated by two independent experts.

Questionnaires

Upon enrolment into the study and after 3, 6, and 9 months, the participants were provided with questionnaires aimed at obtaining information about their state of health (including libido, tension of the breast nipples, disturbances of sexual functions) and effects of Eucapil® on AGA.

Haematological, biochemical and hormonal laboratory examinations

A venous blood sample was taken upon the enrolment and after 6 and 9 months to determine: leukocytes, erythrocytes, haemoglobin, thrombocytes, lymphocytes, monocytes, granulocytes, eosinophils and basophils, further urea, creatinine, ALT, AST, ALP, Ca, Mg, Na, K, Cl, and the total protein.

The serum testosterone and SHBG were assessed upon the enrolment and after 9 months by an RIA method.

The serum was also analysed, using the HPLC method described in (20) in the labs of Interpharma Praha in search of fluridil or its catabolites. The sensitivity of the method was 5 mg/ml.

RESULTS

Only statistically significant results and/or otherwise remarkable observations are described in the following text.

Evaluation of the tolerance

During the study (after 2 and 6 months), 2 patients discontinued because itching and reddening developed at the application site. The remaining 9 females completed the study without any side effects.

Phototrichogram

The percentage anagen/telogen ratio before the treatment and after 6 and 9 months showed no significant changes ($p < 0.05$). The percentage share of anagens

before the treatment was 92.86 %, while the same of telogens was 7.14 %. After 6 months, anagens were 93.13 %, while telogens decreased to 6.87 %. The data after 9 months were 92.69 % for anagens and 7.31 % for telogens.

Hair stem diameter

A statistically significant increase in hair diameter was found after 6 months ($p<0.02$) and after 9 months ($p<0.001$) compared to the baseline values *(Table 1)*. The diameter of hairs increased in 8 of 10 females after 6 months. After 9 months, the diameter of hairs compared to baseline increased in all 9 patients.

Hair surface morphological changes

No pathological or morphological changes were found.

Evaluation of global scalp views

The condition of the scalp hair was evaluated as mildly improved at the end of the study in 6 females (the hair appeared thicker).

Personal questionnaire evaluation

According to the questionnaires, the patients did not refer to any changes in the overall state of health after fluridil application. This confirms the previous findings (*19, 20*) that the topical 2% fluridil is safe, devoid of systemic effects.

The patients' own observations

"Reduced hair loss" was reported by 4 patients after 3 months and by 5 after 6 months. "Improved hair quality" was reported by 1 patient after 6 months and by another one after 9 months. "Reduced greasiness of hair" was observed by 5 patients after 3 months. One patient, who originally indicated a positive opinion about the reduced greasiness, had to be discontinued after 6 months because of skin irritation and extensive dryness at the application site. Further observed changes were "Thickening of the hair" (1 female after 9 months), "New undergrowth" (1 female after 6 months), "Accelerated hair growth" (1 female after 3 months).

Effect of fluridil on biochemical and haematological parameters

The biochemical and haematological parameters studied were within normal range at the enrolment and after 3, 6, and 9 months. No fluridil or its catabolites were found at the level of 5 ng/ml in the serum in any of the samples.

DISCUSSION

To evaluate the efficacy of Eucapil® we used the phototrichogram, which is a non-invasive method. The method is limited in those who show little difference between hair colour and skin colour (phototypes I and V); hence phototypes II – IV were one of the selection criteria for inclusion into the study. Based on the evaluation of the phototrichograms (the anagen/telogen ratio), no effect of fluridil was found,

Table 1

Fluridil increased hair diameter in treated women. Comparison of average hair diameters before the medication (0 month), after 6 and 9 months

Patient		**Average hair diameter**	
code	**0 months**	**6 months**	**9 months**
B. M.	39.68	42.45	40.40
M. B.	59.86	59.29	63.32
R. C.	55.46	56.68	–
I. H.	63.32	67.20	69.49
H. H.	50.17	52.23	59.30
I. K.	52.34	54.62	55.37
D. K.	60.34	66.41	65.20
I. K.	50.87	63.66	63.06
J. M.	56.62	62.15	68.56
P. M.	61.81	61.07	68.45
X	**55.05**	**58.58**	**61.46**
SD	6.42	6.75	8.18
P		0.020	0.001

Table 2

The levels of serum testosterone and SHBG before (0 months) and after (9 months) fluridil medication

Patient code	**SHBG**	**SHBG**	**testosterone**	**testosterone**
	0 months	9 months	0 months	9 months
B. M.	325	218	2.9	1.9
M.B.	190	147	1.1	1.3
I.H.	177	151	2.4	2.0
H.H.	70	74	2.3	4.0
I.K.	347	268	0.6	0.6
D.K.	280	268	1.4	0.9
I.K	223	268	2.4	2.6
J.M.	141	134	1.8	2.5
P.M.	201	258	1.3	0.7
X	217.11	198.44	1.8	1.93
SD	83.36	69.11	0.71	1.09
P		0.322		0.632

Physiological ranges: testosterone 0.2–2.3 nmol/l
SHBG 30–100 nmol/l

unlike in the male study, where fluridil showed the highest efficacy during the first months of the study, perhaps because a gradual blockage of the AR had reached its equilibrium. Continued application of fluridil resulted in limited further improvement (*20*).

This different effectiveness in female AGA can possibly be attributed to cyproterone acetate, which was introduced at least 3 months prior to entering the study (see "inclusion criteria"), but mostly much earlier (the mean period of use was almost 2.5 years). During this long-term treatment with cyproterone acetate inducement of a sufficient antiandrogenic effect can be assumed. This antiandrogenic effect results in reduced hair loss in AGA. The reduction of AGA depends, among others, on the reduction of the telogenic hairs and corresponding increase in the number of anagenic hairs. Normal share of telogenic hairs in healthy subjects reported in the literature is up to 20 % and is influenced by many factors, such as in particular race-related, genetic, and seasonal factors. It is interesting that the percentage share of anagenic hairs in the study group of women, as identified in the baseline phototrichograms, was 92.86 % (ranging from 85.1 % up to 96.6 %). This value is markedly higher than that found in the baseline phototrichograms of men in the above-cited study. This relatively high share of anagens was very probably induced by the previous long-term use of Diane 35®, which is responsible for an extended antiandrogenic effect of cyproterone acetate and effect of oestrogen on the anagen phase prolongation. Thus an additional application of the topical antiandrogen does not induce further improvement of the anagen/telogen ratio. It should therefore appear imperative to conduct a comparative study in AGA females who received no systemic hormonal treatment in the past, but such patients are difficult to find since hormonal therapy in women with androgen-dependent dermatoses including AGA is frequent.

It has been demonstrated that there is a trend for a link between the decrease in hair density and hair diameter in AGA (*22*). The fact that a considerable strengthening of the hair stem occurred during the study in most females is a crucial finding of this study. The thickening was not statistically significant between the 6th and 9th month, but between day 0 and 6 months and 0 and 9 months. The tendency towards further increase in the diameter of hairs was retained during the 6th and 9th month of application. Androgens are known to diminish the size of hair follicles and the hairs growing from those follicles. The strengthening of the hair stem can possibly be attributed to the antiandrogenic effects of topical fluridil, which not only arrests the follicle minimisation, but probably also induced its re-enlargement, which can be deduced from the fact of the significant increase of the hair diameter. The increase of the hair shaft diameter in a woman's long hair is of particular cosmetic benefit (*23*).

According to questionnaires the patients did not report any changes in the overall state of health after application of fluridil. This confirms the previous findings that the topical 2% fluridil is safe, devoid of systemic effects (*19, 20*).

One half of the patients reported reduced greasiness of hair from the first 3 months of application. This effect seems to be associated with the reduced sebum production due to the antiandrogenic effect of fluridil on the sebum glands. The drying effect of the alcohol vehicle (isopropanol) on the skin is probable. It is

interesting that half of all patients (except for one) observed reduced hair loss as soon as within 3 months. This correlates with our previous observation with fluridil AGA in men, where the highest increase of anagens was observed after 3 months of application.

Topical application of fluridil produced no changes in the laboratory findings and no fluridil was detected in the serum at the level of the method sensitivity (5 ng/ml).

The levels of serum testosterone before the enrolment were only slightly increased in 3 patients. This finding corresponds with previous reports that there is usually no excess of serum androgens in women and men with AGA. Moreover, the values of serum testosterone in our patients were influenced by CPA treatment. The increased levels of serum SHBG are common in women taking COC, which was the case for 8 out of 9 patients in our study. There were no statistically important differences between the levels of serum testosterone and SHBG before and after fluridil treatment, evaluated by a paired t-test (*Table 2*).

In the 2 women who discontinued the use due to skin irritation, the epicutaneous tests excluded allergic contact reaction, suggesting the irritation to be attributable to the vehicle.

CONCLUSION

The topical antiandrogen fluridil is a safe and effective alternative in the AGA treatment not only in men, but also in women, in whom long-term regular application of Eucapil® enlarges the hair stem diameter, thus improving the appearance, and arrests the progression of AGA. The product can be used both in monotherapy and in women also in combination with systemic hormonal treatment to potentiate the curative effect.

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SOUČASNÁ LÉČBA ANDROGENETICKÉ ALOPECIE U ŽEN A VYUŽITÍ NOVÉHO LOKÁLNÍHO ANTIANDROGENU FLURIDILU

Souhrn

Androgenetická alopecie (AGA) je nejčastější formou alopecie. AGA je androgen-dependentní proces, při kterém dochází k miniaturizaci vlasových folikulů u geneticky predisponovaných mužů a žen. V současnosti je AGA u žen léčena obvykle zevně minoxidilem, a na rozdíl od mužů také systémově podávanými antiandrogeny. Prořídnutí vlasů u žen je obvykle méně výrazné než u mužů, nicméně u žen způsobuje AGA závažné psychické problémy. Proto jsou žádoucí nové bezpečné a účinné postupy v léčbě AGA. Fluridil byl vyvinut jako lokální antiandrogen, vhodný k léčbě hyperandrogenních kožních syndromů. Kosmetický produkt Eucapil®, obsahující 2% fluridil v isopropanolu, byl testován u žen s AGA v 9měsíční otevřené klinické studii. Do studie bylo zařazeno celkem 11 žen (průměrný věk 35 let) s I.–II. stupněm AGA podle Ludwiga. Růst vlasů byl hodnocen pomocí fototrichogramů. Procentuální poměr anagenů/telogenů po 6 a 9 měsících nevykazoval statisticky signifikantní změny ($p<0.05$), ale po 9 měsících nedošlo k progresi AGA.

Měření průměru anagenního vlasového stvolu pomocí optické mikroskopie ukázalo statisticky signifikantní zvýšení po 6 měsících ($p<0.02$) a po 9 měsících ($p<0.001$). Metodou skenovací elektronové mikroskopie nebyly nalezeny žádné morfologické změny. Dvě pacientky studii přerušily kvůli podráždění kůže v místě aplikace, které bylo způsobeno isopropanolem. Nebyly nalezeny změny v biochemických nebo hematologických hodnotách a vyhodnocení dotazníků svědčí pro to, že aplikovaný Eucapil® nevykazuje systémové účinky. Eucapil® je díky své bezpečnosti a účinnosti lákavou alternativou v léčbě AGA u žen.

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

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