Fluridil (Eucapil®) in Female Androgenetic Alopecia: Efficacy and Safety after 9 months Use

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A new suppressor of the androgen receptor (AR), fluridil, was developed for topical treatment of hyperandrogenic skin syndromes. Owing to its hydrophobic properties and formulation in isopropanol (rubbing alcohol), it is hypothesized that fluridil readily dissolves in the sebum and diffuses into the follicle. Fluridil was designed to decompose in an aqueous environment into pharmacologically innocuous and hormonally inactive fragments ***(Fig. 1)***, which are rapidly eliminated. During human studies neither fluridil nor its decomposition products were detected in serum at or above the detection limit of 5 ng/ml. In 40 male AGA patients, fluridil significantly increased the anagen/telogen ratio and all biochemical and hematological parameters were within normal range. No irritation potential of fluridil was found in a 21-day test on 20 human volunteers (Sovak et al., 2002; Seligson et al., 2003).

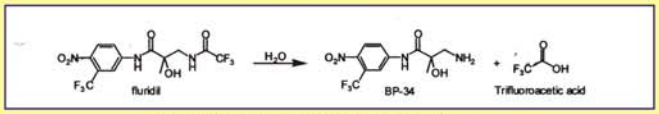

Fig.1. Fluridil and its hydrolytic decomposition

Material and methods

The efficacy and safety of 2% fluridil solution in anhydrous isopropanol (Eucapil®, manufacturer Interpharma Praha, a.s.) was tested in an open clinical study involving 11 females with AGA (6 with stage I, 5 with stage II, according to Ludwig), age range 22 to 45 years (average age 35). The inclusion criteria were: phototype II-IV, androgenetic alopecia stage I-II according to Ludwig ***(Figs. 2, 3)***, administration of Diane 35 (a combination of cyproterone acetate and ethinylestradiol) started at least 3 months prior to the enrollment, no other systemic or external treatment of AGA at least one month prior to enrollment. 2 ml Eucapil® was gently massaged into the dry scalp, once a day, in the evening.

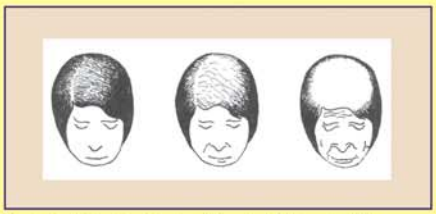

Fig.2. Ludwig´s classification of female AGA (grade I-III)

Fig. 3. Clinical findings of female AGA (grade II)

Clinical assessment
The effect on AGA was evaluated independently by the physician and by the participant using the scale: 0=excellent, 1=good, 2=none, 3=aggravation, after 3, 6 and 9 months of fluridil treatment. Tolerance was evaluated as 0=excellent (no adverse effects), 1=good (less recognizable adverse effects, not constituting a reason for discontinuation of the therapy), 2=poor (severe adverse effects, constituting a reason for discontinuation of the therapy). A point score was calculated as the mean of all participants for the given interval.

Phototrichograms before and after 6 and 9 months
The phototrichograms ***(Fig. 4)*** were obtained by photographing a predefined area immediately after shaving and counting the hair follicles. Follow-up photographs and counts were obtained after 72 hours. The anagens/telogens were identified: the hair in the linear formation having the length of approximately 1.2 mm are in the growth phase, i.e. anagens, while the non-growing hair in the resting phase are telogens.

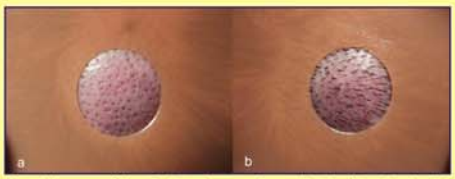

Fig. 4 Images of identical scalp areas immediately after shaving (a) and after 72 hours (b)

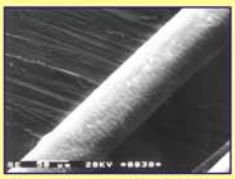

Fig. 5 Hair scanned by EM after 9 months of daily fluridil (Eucapil®) (normal structure)

Hair stem diameter measurement
Before the study onset, approximately 50 recently grown hairs (3 weeks) in the anagen phase were collected from a round area of about 1.5 cm diameter in the frontoparietal region. A Carl Zeiss Jenamed microscope with Kontron image analyzer (Germany) and a 20× planachromatic lens was used for the measurements. 10 diameters within the 5-10 mm sections of each hair stem were read. A total of 40 hairs were measured for each sampling, in every participant, at every time interval.

Hair surface morphology
Five hairs from each participant were glued and then metal-coated using an E 5100 Polaron (Great Britain) coating unit. A scanning electron microscopy (SEM) (Tesla BS 340 microscope) was used to analyze the hair surface morphology.

Global scalp images
Photo images were taken from above and evaluated for differences by two independent experts.

Questionnaires
Upon enrollment and after 3, 6 and 9 months, the participants completed a questionnaire aimed at determining their state of health, their previous experience with other AGA therapies and their subjective observation of the effects of Eucapil® on AGA.

Hematological and biochemical laboratory examination
Leukocytes, erythrocytes, hemoglobin, thrombocytes, lymphocytes, monocytes, granulocytes, eosinofils and basofils. Serum levels of urea, creatinine, ALT, AST, ALP, Ca, Mg, Na, K, Cl and total protein.

Results and discussion

Clinical assessment
Participants completed the study without any side effects. In all subjects, the effluvium stopped after about two to three weeks of use. Two patients discontinued participation due to reddening, itching, and dryness at the application site. The standard epicutaneous test conducted by us excluded an allergic mechanism: Fluridil was found to have no sensitizing potential confirming the previously reported results (Seligson et al., 2003). The skin irritation is thus attributable to isopropanol, the "rubbing alcohol" known to irritate the skin, especially if it has been previously deprived of the skin fat by excessive washing .

Phototrichograms
Before treatment the percent anagens and telogens of the total hair count were 92.86% and 7.14% respectively. After 6 months, anagens increased to 93.13% while telogens decreased to 6.87%. After 9 months 92.69% anagens and 7.31% telogens were found. These changes were not statistically significant ($p < 0.05$), but that could be expected since the normal ratio of anagen/telogen is about 80/20 and our clinical sample was in that sense unusual, probably owing to previous administration of Diane-35.

Hair stem diameter evaluation
There was a substantial and statistically significant increase in the hair diameter both after 6 months (6.4%) ($p<0.02$) and after 9 months (11.6%) ($p<0.001$) (Table 1). After 6 months, the diameter increased in 8 of 10 participants. After 9 months, an increase was observed in all 9 participants. The increase during the 6th and 9th month was, however, not statistically significant.

The increase in hair stem diameter together with the arrest of effluvium appears to be the substantial finding of this study. Application of fluridil improves the global appearance of the hair.

Androgens are known to diminish the size of the hair follicles and also to thin the hair. The strengthening of the hair stem is attributed to the anti-androgen effect of fluridil, which reverses unwanted follicle reduction. The significant increase of the hair diameter is probably the result of improved follicle function.

Table 1. Fluridil increased hair diameter in treated women. Comparison of average hair diameters before (0 month) and after 6 and 9 months.

Participant		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

Hair surface examination
Examination of the hair surface by SEM before and after Eucapil® administration displayed no visible changes (***Fig. 5***).

Evaluation of the global scalp views
The condition of the scalp was evaluated as mildly improved at the end of the study in 6 participants (their coiffure appeared more substantial), and no effluvium or progression of AGA was observed.

Questionnaires
No systemic effects of Eucapil® (fluridil) were reported.

Effect of fluridil on biochemical and hematological parameters
The biochemical and hematological parameters were within normal range in all participants before and after 3, 6 and 9 months of study.

No fluridil nor its metabolites or products of decomposition were found in the serum using the HPLC method with detectability limit of 5ng/ml (Sovak et al., 2002).

Conclusion

The topical anti-androgen fluridil, previously tested in AGA treatment in men, proves to be safe and effective in female AGA. The long-term regular daily application of Eucapil® increased the hair stem diameter and thus improved the global appearance, and arrested AGA progression. The product can be used both in monotherapy and in women also in combination with systemic hormonal treatment to potentiate the curative effect.

References

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