

# TREATMENT OF HIRSUTISM

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## Synopsis

The hormonal sources of hirsutism to a great extent go back to increased local androgen metabolism in the skin. Elevated androgen receptor binding sites in hirsute areas of body hair as well as elevated peripheral androgens contribute to the overstimulation of the androgen dependent hair follicles.

Prior to treatment of hirsutism a careful hormonal investigation should evaluate the origin of hyperandrogenaemia in order to establish a causative treatment.

Antiandrogens act by blocking the androgen receptors in skin tissue. Besides, they may suppress serum androgens.

Cyproterone acetate (CPA) can be applied in various dosages.

Besides a monthly, parenterally applied bolus CPA showed good effects and minimal side effects.

Other antiandrogens - spironolactone and cimetidine - are not convincing as mono-treatment and should be preserved for additional therapy in severe cases.

Medroxyprogesterone acetate implantants show good effects by 6 weekly intramuscular application or intracutaneous injection into hairy areas and is mainly apt for menopausal females.

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## Riassunto

In linea di massima a livello ormonale l'irsutismo provoca un aumento del metabolismo cutaneo locale degli androgeni. Nelle aree affette da irsutismo l'elevata presenza degli androgeni periferici e dei relativi siti recettoriali contribuisce alla elevata stimolazione dei follicoli piliferi androgeno dipendenti. Prima di iniziare il trattamento dell'irsutismo deve essere condotta un'attenta disamina ormonale per ben valutare l'origine dell'iperandrogenia.

Gli antiandrogeni agiscono bloccando i recettori ormonali presenti a livello cutaneo.

Il ciproterone acetato (CPA) puo' essere applicato a vari dosaggi. L'applicazione parenterale mensile di un bolo di CPA ha mostrato una buona efficacia accompagnata da minimi effetti collaterali. Altri antiandrogeni-spironolattone e cimetidina non convincono nel monotrattamento e dovrebbero essere utilizzati soltanto come coadiuvanti terapeutici nei casi piu' gravi. L'impianto dell'acetato di Medrossiprogesterone mostra buoni risultati dopo sei settimane sia se effettuato intramuscolo che sottocutaneo direttamente nelle zone affette, soprattutto nelle donne in menopausa.

## Introduction

The clinical aspect of facial and body hair distribution shows broad individual variations due to racial, genetic and hormonal influences. Hirsutism is the overgrowth of hair in sex hormone dependent areas of facial and body hair under increased androgenic influence. In the face the chin, the submental region, the cheeks and the upper lips are mainly involved. On the body of sites predilection are the presternal and circumareolar regions and the abdomen. The density of pubic hair is nearly always increased in hirsute women and the hair mostly extends to the inner parts of thighs.

Regulation of hair growth is modulated by complex interactions of multiple - also hormonal - influences on the different structures of the hair follicle and the dermal papilla. Hamilton (1) showed as early as 1942 that hair follicles are active target sites of testosterone. Plucked hair follicles were shown to metabolize testosterone. Fazekas and Sandor were the first to demonstrate androgen receptors in pilary roots (2). These observations confirmed the role of the hair follicles not only as endocrine targets but also as active sites of androgen metabolism. Androgens seem to interact with all of the compounds that are responsible for hair growth. By elongation of the growth phase the previous thin, medulla and pigment less vellus hair is transformed into the medullated, pigmented and thick terminal hair in androgen dependent areas, which is characteristic of hirsute aspect.

Although the stimulatory effects of androgens on androgen dependent hair roots are well described, the percentage of elevated androgen serum levels in hirsutism varies between 90% elevated (3, Kirschner & al) and normal range levels (4, Korenman & al.). Hirsutism in females with normal androgen levels is the so-called "idiopathic hirsutism". Determination of androgen receptors allows conclusions about the androgen stimulability of the target organ - the skin tissue.

## Studies and results

In our studies of hirsutism in 36 females androgen receptors (AR) were determined by saturation analysis and found to be abnormally high in 26%. The mean AR level was 68 /fmol/mg protein and thus almost 8 times higher than in normal skin and 3 times higher than in acne (5, Schmidt & Spona, 1985). The endocrine profile showed elevations of Testosterone (T) in 63%, Dehydroepiandrosterone - sulfate (DHEA-S) in 50% and Androstenedione (A) in 37% of the patients. Moreover, the missing correlation between androgen serum levels and AR indicated an autonomous hormone metabolism at the receptor level.

These results show that both elevated androgens and increased AR binding may contribute to hirsutism. The most effective treatment thus aimed at both levels, the hormonal as well as the cellular.

If the androgen constellation indicates an ovarian source of hyperandrogenaemia, the extent of the androgen elevations (testosterone, androstenedione) determines further diagnostic or therapeutic steps. Of course, in severe cases polycystic ovary syndrome has to be excluded prior to any hormonal treatment. In the other cases antiandrogens can properly be used to suppress the increased hormone levels and the block the AR binding sites.

Of all available substances, cyproterone acetate is clinically the most promising substance. The low dose cyproterone acetate treatment (Diane: 2 mg CPA + 50 or 35 µg E<sup>2</sup>/pill) is a successful regimen for the treatment of moderate hirsutism, but has the disadvantage of late onset of the therapeutic effects. By additive application of 50 mg cyproterone acetate (Androcur) from day 5 to 15 of the menstrual cycle the effects are increased.

Recently, improved effects had been reported by a once monthly parenteral application of a bolus of 300 mg CPA (6, Moltz & al). In our study the

effects of 100 mg cyproterone acetate administered daily perorally for the first 10 days of menstrual cycle have been compared with those of a once monthly implant of 300 mg cyproterone acetate on the first day of each cycle. 10 patients with severe hirsutism were recruited for each treatment. Additionally, contraception was maintained with Diane in both groups.

The clinical effects, consisting of reduced hair growth and thinning of hair, decrease of pigmentation and prolongation of the intervals between epilatory measures, were noted in both groups from 3 months of treatment onwards.

Side effects consisted mainly of breast tension, nausea and menstrual disturbances.

Clinically, parenteral administration of cyproterone acetate appeared slightly more effective than oral administration (7, Schmidt, Huber, Spona).

As well as the classical antiandrogen, cyproterone acetate, also antiandrogens such as spironolactone and cimetidine have also been claimed to provide beneficial effects in hirsutism. In our experience, spironolactone should be administered only in cases which show therapeutic resistance to other substances. Although the effects of treatment show rapid onset, they also diminish after few months. Regular controls of the electrolytes, which often are responsible for severe side effects are requested if treatment is performed in adequate dose (2x100 mg/d).

Cimetidine is the weakest antiandrogen and therefore should only be administered for moderate forms of hirsutism or as additional treatment, in a dosage of at least 3x400 mg/day. Another promising but less well-known substance is medroxyprogesterone acetate (MPO). The Depot-Gestagen acts by inhibition of the enzyme 5 $\alpha$ -reductase which converts T to DHT and by a decrease of serum androgens. For comparison of systemic and local effects of the substance 3 forms of application were carried out in a group of 26 females with moderate hirsutism

for a mean of 16 weeks: 150 mg MPO was administered as an intramuscular implant or as intralesional injections into hairy areas of the face in 6 weekly intervals. A third group of patients applied a 0.2% MPO containing ointment on the hairy sites of the face. As before, clinical changes were noted and hair measurements were made. The comparison of these parameters revealed that the best results were achieved by the intralesional application of MPO into the hairy areas where both the local and systemic effects of MPO contributes to the action. Next best was parenteral application where the systemic effects predominate. However, the local ointment also showed positive effects, thus confirming a peripheral action of MPO at the tissue level, as no decrease of serum androgens was shown. Side effects consisted mainly of menstrual disturbances (8, Schmidt & Spona, 1985). In menopausal hirsute women, especially MPO treatment is of great benefit, as it also displays beneficial effects on menopausal symptoms.

## Discussion

A range of substances, broader than in former years, allows more specific and individual treatment of hirsutism than previously. Detailed determination of the hormone parameters should help to clarify the source of hyperandrogenemia and should precede the decision on hormonal treatment.

Adequate treatment may sometimes include a combination of various hormonal substances adapted to the individual hormone profile. New developments of merely topically active androgens could mainly amplify the endocrine treatment of hirsutism and permit effective therapy without side effects in cases in which serum androgens are normal.

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