CYPROTERONE ACETATE

Professor J. Hammerstein

Introduction

Cyproterone acetate (CPA) is at present the only anti-androgen that has reached the stage of clinical application and general acceptance in several continental countries. This statement needs qualification in so far as other closely related compounds that have a 17∝-acetoxy-progesterone structure, which have been much used in hormonal contraception, are also supposed to exert slight anti-androgenic effects in man.

Chlormadinone acetate, which is structurally closely related to CPA, must be specially mentioned here since this strong progestogen has been preferentially utilised as the progestational component of oral contraceptives in the treatment of androgenised women, at least in Germany. To judge from animal experiments its anti-androgenicity is distinctly weaker than that of CPA (Wiechert et al. 1967). However, comparative studies in man are lacking.

Limited clinical experience also exists with benorterone, the first anti-androgen tried in man, and with free cyproterone. In the late sixties benorterone was reported to give promising results in 93 androgenized women but was soon withdrawn from clinical trial, mainly because of the development of gynaecomastia in the male. As a big advantage compared with CPA, it was found to be effective not only orally but also topically. Free cyproterone, on the other hand, proved to be without clinical value for reasons that cannot be discussed here. Thus we are left with CPA as the only anti-androgen that is already on the market in several countries.

Clinical Pharmacology

CPA may be characterized endocrinologically as possessing strong progestational, moderate anti-androgenic and limited anti-gonadotropic potencies. In addition, a corticoid-like activity has been postulated recently.

Its progestational activity, in terms of the transformation dose in the oestrogen-primed human endometrium, is 20-30 mg. which is

comparable to that of chlormadinone acetate and other strong progestogens (Table I). To take full clinical advantage of its anti-androgenicity not less than 50-100 mg. CPA must be taken orally per day, which totals 2 to 3 times the progestational activity the female organism is exposed to throughout a complete ovulatory menstrual cycle. Thus unless much lower and less efficacious doses of CPA are used, a tremendous progestational overdosage must be accepted.

TABLE 1

Progestational Potency of Some Contraceptive Progestogens in the Human

	Transformation Dose mg./Cycle	Menses Delay Test mg./Day
Progesterone	200 i.m.	1,000
Medroxyprogesterone acetate	40 - 70	20 - 30
Megestrol acetate	35 - 50	5 - 10
Chlormadinone acetate	20 - 30	4
Cyproterone acetate	20 - 30	
Norethynodrel	150 - 200	14
Norethindrone	100 - 150	15
Norethindrone acetate	50 - 60	7.5
Lynestrenol	35 - 70	10
Ethynodiol diacetate	10 - 15	1
d-Norgestrel	6	5

According to Giusti et al. (1977) application of 100 mg. CPA daily from Day 5 to 25 of the cycle abolished the ovulatory peaks of blood LH and FSH in each of 5 normal women. The response to GnRH was also diminished during this treatment. In the male,

unlike the female, the anti-gonadotropic potency of CPA still is a matter of controversy.

High dosage CPA treatment in children has been reported to lead possibly to an inhibition, or even to a complete suppression, of both pituitary ACTH and adrenal cortisol secretion, although clinical signs of adrenal insufficiency or of sudden collapse have not been noted so far. These findings, which were first published by Girard and Baumann (1975) and later confirmed in Berlin by von Muhlenahl et al. (1977) are now under further investigation in several places. A cortisol-like action of CPA has been postulated in order to explain the absence of signs of adrenal insufficiency.

Until now no similar observations have been made in adults. This may be due, among other things, to the much lower dose of CPA administered per kg. body weight and/or to the adrenals of adults being fully developed at the onset of treatment. To illustrate this, the example of two adult patients with congenital adrenogenital syndrome is given who were placed on 100 or 200 mg. CPA daily after stopping standard corticoid therapy (Fig. 1). In both cases urinary excretion of the 17-ketosteroids and 17-hydroxysteroids quickly increased, in one case almost to the pre-treatment levels of the latter after 3-4 weeks. At the same time acne and seborrhoea reappeared, thus indicating that the central and/or adrenal suppressive effect of CPA, if there is any, was not strong enough to substitute for corticoids. This endocrine disturbance is the only clinical entity in connection with hirsutism in which treatment with corticoids is distinctly superior to CPA.

This view if further supported by the finding that a drop in blood cortisol and/or urinary 17-hydroxysteroids to very low values has never been observed in virilized women under low - or high - dose CPA treatment (Fig. 2). The moderate decrease in the 17-hydroxysteroids under CPA medication is comparable to that occuring when other oral contraceptives are taken. Recently Smals et al (1978) were unable to find any major change in the plasma levels of ACTH and cortisol or in the adrenal responsiveness to ACTH in 10 patients under 100 mg. CPA taken cyclically without oestrogens.

There is a high avidity of adipose tissue for CPA leading to a pronounced depot effect, which is another peculiarity that has to be taken into account when this compound is being used in man

17-KETOSTEROID AND 17-HYDROXYSTEROID EXCRETION IN URINE IN 2 PATIENTS WITH AGS UNDER DIFFERENT THERAPY REGIMENS INCLUDING CYPROTERONE ACETATE

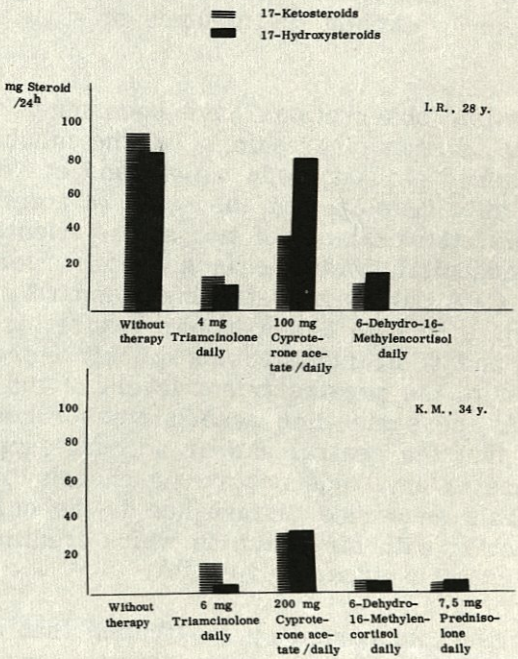


Fig. 1

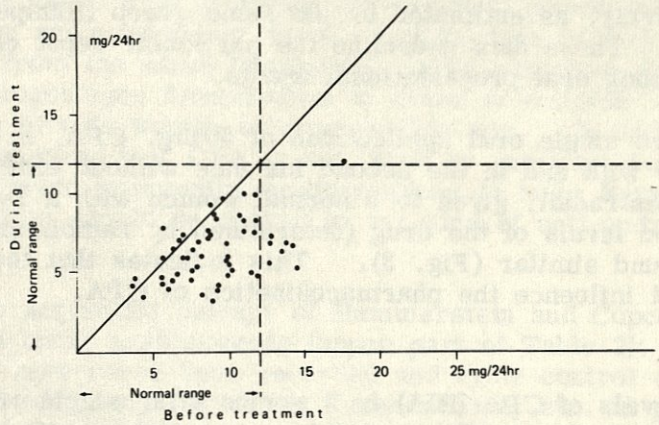


Fig. 2 Correlation between urinary 17-hydroxysteroid excretion before and during CPA/EE standard treatment (55 patients). Hammerstein et al. 1975.

in high doses. On the basis of intensive pharmacokinetic studies it was concluded by Hümpel et al. (1977a) that it is the reabsorption of CPA from the tissue and maybe its metabolism, rather than the elimination of CPA or its metabolic products, that is rate - limiting and thereby responsible for the depot effect under discussion. Thus the apparent volume of distribution of CPA has been estimated to be 10 times larger than that of its main metabolite 15β-OH-CPA. In other words, 90% of the compound stays unchanged in the body at any time after administration; and this appears to be true for both males and females.

In women, pharmacokinetic studies have been published only with the low-dose formulation, which consists of 2 mg. CPA and 50 µg ethinyloestradiol (Hümpel et al. 1977a). Intestinal resorption was found to be complete and postmaximum disposition of CPA to take place in two phases with blood half-lives of 3.0 ± 1.3 hours and 2.0 ± 0.4 days respectively, the latter value being distinctly greater than that found in the male. The difference may be due to the sex-dependent difference in the size of the adipose tissue.

For comparison, the second disposition phases for levonorgestrel and lynestrenol were only 1.1 ± 0.3 d. and 0.69 ± 0.03 d. respectively, as estimated by the same group (Hümpel et al. 1977b). These data underline the particular depot character of CPA among oral progestational agents.

After two single oral applications of 50 mg. CPA, in the first instance with and in the second instance without additional 50 µg ethinyloestradiol, given to 5 normal women with a 7-day pause, the blood levels of the drug (determined by radioimmunoassay) were found similar (Fig. 3). This indicates that the oestrogen does not influence the pharmacokinetics of CPA.

Blood levels of CPA (RIA) in 5 women after single oral applications of two CPA containing preparations with a 7-day pause (Moltz et al. unpublished) Mean ± Standard Error

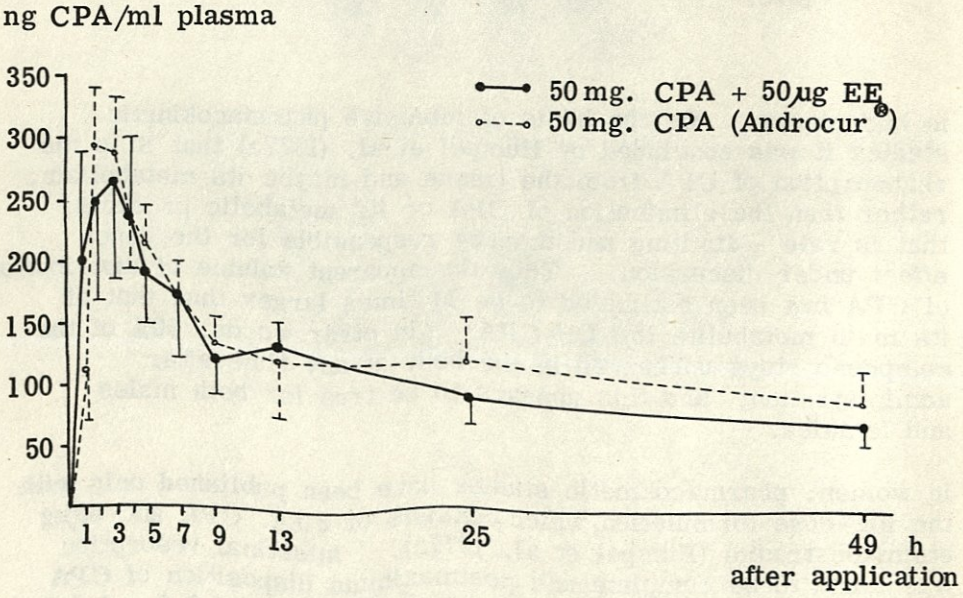


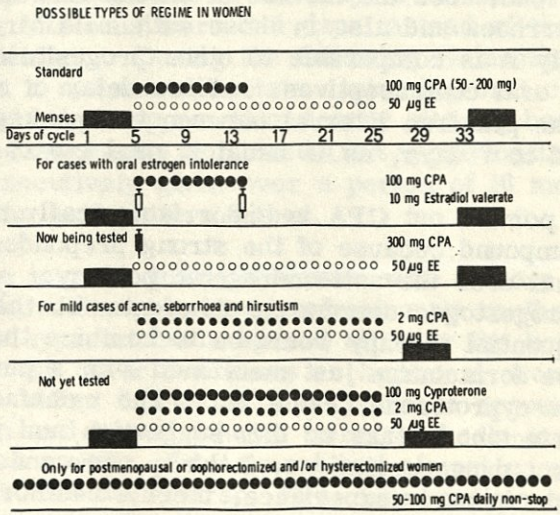
Fig. 3

Modes of CPA application in women (Table 2)

The combination of high progestational potency, moderate anti-androgenicity and pronounced depot effect present in CPA requires a deviation from the usual therapeutic cyclic schedules for oestrogen/progestogen formulations in order to maintain cyclic bleedings in hirsute women of reproductive age. In addition, it must be ensured that CPA is not taken by pregnant women in order to avoid intersexual malformations in male fetuses. This precaution should be obeyed in any kind of anti-androgen treatment.

The reverse sequential therapy of Hammerstein and Copceancu (1969) meets these requirements (upper part of Table 2): pregnancies have never been recorded and cycle control with regard to breakthrough bleedings, amenorrhoea, etc. in general is excellent.

TABLE 2



However even with the limitation of the CPA-intake to days 5 until 14 of the treatment cycle the depot effect of the drug is usually strong enough to delay the onset of withdrawal bleeding to 4-5 days after the last oestrogen has been taken. In adipose patients the delay is still longer. In patients with such a protraction of the withdrawal bleeding, shortening of the CPA administration from 10 to 8 days may become necessary whilst the oestrogen intake over the full period of 21 days should not be changed. Because of this prolongation of the treatment cycle it is advisable to deviate from the general rule in oral contraception and to tell the patient not to start the new therapeutic course before day 5 of the next cycle.

In cases with oral oestrogen intolerance, the oestrogen may be given parenterally, for example 10 mg. oestradiol valerate twice per cycle (see Table 2). Substitution of the oral by the parental route of CPA administration is presently under investigation by our group and initial results are encouraging.

Recently an oral contraceptive came on to the German market which contains 2 mg. CPA and 50 µg ethinyloestradiol per pill. This combined preparation, which contains only 1/24 of the CPA content in the reverse sequential formulation, should at present be considered the method of choice in women with acne and/or seborrhoea and also in those with mild hirsutism. Quantitatively it is comparable to other progestationally accentuated oral contraceptives. Since delay of menses is negligible the pill-free interval between two packages can be standardized to 7 days, as is usual in oral contraception.

As already pointed out CPA is endocrinologically not a well-balanced compound because of the strong preponderance of the progestational over the anti-androgenic potency. A way to avoid the heavy progestogen overdosage inherent with the high-dose reverse sequential therapy would be to combine the low-dose contraceptive formulation just mentioned with a pure anti-androgen such as free cyproterone (Table 2). The manufacturers are however, reluctant to take up this suggestion and with respect to the present drug regulations, I think, one cannot blame them. According to my early experience, uterine haemorrhages are inevitable when CPA is given without oestrogens over a long period of time, unless the patient is post-menopausal, oophorectomized or hysterectomized. Only in these rare cases may the supplementary administration of oestrogens be omitted.

Therapeutic results

Turning to our clinical observations, three case reports will be mentioned at first in order to illustrate to what extent hirsutism can improve under the high-dose reverse sequential therapy. Endocrinological details and photographs of the patients are given elsewhere (Hammerstein et al. 1975).

Example one is a 39 year old subtotally adrenalectomised woman with progressive hirsutism of ovarian origin. After 10 months of treatment the severe hirsutism on the breasts, the linea alba and the thighs had almost completely disappeared, except for the beard which made shaving necessary at weekly intervals instead of shaving every second day before treatment. In our experience this is nearly a rule: the more shaving, or other kind of mechanical or chemical removal of body hair, the less the therapeutic success. Within 7 months after cessation of treatment hirsutism gradually reappeared but not anywhere to the pre-treatment intensity.

Example two is a 37 year old woman with severe progressive hirsutism which was classified as adrenal in origin. After 12 months of reverse sequential therapy again the hirsutism had almost entirely disappeared in all body areas except the face where shaving intervals were 3-4 days instead of the 2 days pre-therapeutically. During the following 14 months of treatment with a megestrol acetate containing oral contraceptive hirsutism distinctly reappeared and daily shaving became necessary. Low-dosage combined CPA/ethinyloestradiol treatment consecutively given over a period of 16 months did not improve the hair pattern either.

Example three is a 22 year old woman with a more stable type of idiopathic hirsutism, located predominantly on the face but combined with hypertrichosis spread all over the body. In contrast to the other two cases no hormonal anomalies were discernable. After 8 months of the reverse sequential therapy both hirsutism and hypertrichosis were markedly improved and after another 8 months of treatment had almost completely disappeared. Blonde, sparse, fine, intermediate-type hair were the only remnants of the previously severely increased body hair. Two years after cessation of CPA medication the body hair pattern had almost returned to the pre-treatment state.

It is clear from these three examples that hirsutism may respond favourably to CPA administration irrespective of its cause. In general, however, patients with idiopathic hirsutism are not such good candidates for treatment with CPA as women with ovarian and/or adrenal hyperandrogenisation. It is also obvious that after cessation of the anti-androgen therapy hirsutism usually tends to reoccur quickly. Only in one third of a limited number of cases evaluated by my colleague Professor Zielske did body hair not increase during the first 9 months after termination of treatment whereas this was true for two thirds of patients if CPA treatment was followed by oral contraception with a 17α-acetoxyprogesterone containing pill (Table 3).

Not all virilized women respond satisfactorily to high-dose CPA administration (Table 4). Observations from five endocrinological centres in Germany revealed that 20-35% of hirsute patients failed to react adequately to this treatment (Hammerstein et al. 1975). It is unclear why this happens in one case but not in another since evidence for differences between the two groups of patients in endocrine status before and during treatment and also in the body hair distribution is lacking. Unpublished pharmacokinetic studies performed by my colleague Dr. Moltz point to the possibility of slight differences between responders and non-responders with regard to CPA blood levels. Whether this is sufficient to explain the failure of treatment in almost one third of the patients is doubtful and makes further investigation necessary.

It is also noteworthy from this compilation of data that hirsutism rarely improves before the 3rd month of treatment and that usually 9 months of medication are needed before the final clinical result is achieved. Trichometrically, changes in the hair shaft diameter are discernable earlier.

The reverse sequential therapy is generally well tolerated. Among the side effects, tiredness, lassitude, loss of libido and breast discomfort predominate (Table 5). Other complaints are observed at a similar rate as in oral contraception. It is our experience that patients with weight gain outnumber those with weight loss only insignificantly.

Finally a few remarks are necessary concerning the low-dose CPA/ethinyloestradiol combination formulation (Table 2) which - not surprisingly - is distinctly inferior to the high-dose reverse sequential therapy if tested in the same patient. About 50% of

TABLE 3

Clinical Course in 76 Hirsute Women After Stopping Reverse Sequential CPA/EE Therapy

(According to F. Zielske et al. 1971)

Further Treatment	Final Result of CPA Treatment	Months after stopping CPA Treatment				Summary
		1 - 3	4 - 6	7 - 9	9	
None	Maintained	6	4	3	2	15
	Change for the Worse	11	6	2	6	25
Oral Contraceptives with Megestrol Acetate or Chlormadinone Acetate (Planovin, Aconcen, Oraconal)	Maintained	3	11	3	8	25
	Change for the Worse	5	5	-	1	11

TABLE 4

Clinical results of the CPA/EE standard treatment in correlation with the duration of medication (Findings of five endocrinological centres for 602 patients)

		Distinct beneficial effect in % of all cases treated for indicated time				Total
Length of treatment (months):		3	6	9	> 9	
Hirsutism	Dusseldorf	65%	55%	77%	80%	102
	Frankfurt	-	-	28%	-	11
	Hamburg	30%	80%	86%	76%	97
	Ulm	-	-	89%	-	44
	Berlin	12%	43%	56%	65%	136
	Total	23%	50%	60%	69%	390
Acne	Dusseldorf	87%	75%	67%	71%	44
	Frankfurt	-	-	100%	-	3
	Hamburg	86%	82%	100%	100%	42
	Ulm	-	-	-	100%	15
	Berlin	61%	89%	97%	97%	71
	Total	68%	87%	95%	96%	175
Seborrhoea	Dusseldorf	87%	76%	59%	69%	77
	Frankfurt	-	-	-	-	-
	Hamburg	80%	100%	100%	100%	18
	Ulm	-	-	-	100%	1
	Berlin	63%	86%	94%	94%	64
	Total	69%	84%	87%	89%	160
Androgenic Alopecia	Dusseldorf	66%	33%	75%	50%	32
	Frankfurt	-	-	0	-	2
	Hamburg	17%	25%	0	100%	15
	Ulm	-	-	-	50%	6
	Berlin	7%	14%	23%	40%	44
	Total	19%	16%	26%	45%	99

TABLE 5

Side effects under CPA/EE standard treatment

(Findings of five endocrinological centres for 602 patients according to Breckwoldt, 1972)

Tiredness, lassitude	:	132	22.0%
Increase in body weight	:	86	18.5%
Loss of libido	:	60	10.0%
Breast discomfort	:	55	9.2%
Nausea	:	54	9.0%
Headache	:	44	7.3%
Depression	:	31	5.1%
Irregular uterine bleeding	:	22	3.5%
Sleep disturbance	:	22	3.5%
Thrombophlebitis	:	6	1.0%
Chloasma	:	5	0.9%
Constipation	:	3	0.5%
Thrombosis	:	1	0.15%

non-responders to this low-dose preparation still gave good results when subsequently placed on the high-dose formulation (Table 6). If, on the other hand, virilised patients with good response to the high-dose are later placed on the low-dose medication hirsutism gets worse in about 60% of cases.

Nevertheless, in 50% of patients with mild hirsutism the CPA content in the low-dose contraceptive preparation is large enough to give satisfactory results when taken permanently. In cases with severe hirsutism, on the other hand, this treatment usually fails to improve virilism sufficiently. While it may be predicted that the low-dose CPA containing formulation is superior in reducing hirsutism to other ovulation inhibitory contraceptive preparations, no reliable clinical data are available on this issue at present.

Conclusions

In conclusion, with CPA becoming available for clinical purposes post-pubertal hirsutism is open to medical treatment for the first time. At present, high-dose reverse sequential therapy should be considered the method of choice in severe hirsutism wherever CPA is available. In mild cases, initial treatment should be with the low-dose combination formulation. Since clinical improvement of hirsutism is usually not maintained after cessation of treatment it is advisable to tentatively reduce the CPA dose stepwise or to place the patient straight on to the low-dose preparation as soon as the final therapeutic result has been achieved. With the reduction of the CPA dose it is aimed to diminish such side effects as tiredness, lassitude and loss of libido which are supposedly related to the progestational potency of the drug. It must be emphasized that CPA is far from being an ideal drug for the anti-androgenic treatment of hirsutism because its progestational potency is much too strong and it is not effective when administered topically. Therefore it is worthwhile looking for better-balanced anti-androgenic compounds for the future.

Long-term cures after only transient CPA administration are rather rare and patients even after years of treatment - in one of my cases 12 years - often do not show a reduction or delay in the reappearance of hirsute symptoms after discontinuation of the medication. Sooner or later, therefore, the treating physician is faced with the problem as to how long he can justify such a treatment in view of the increasing danger to health with age.

TABLE 6

Comparison of the therapeutic efficacy of high- and low-dose CPA treatment in virilized women (According to Moltz et al. 1978)

Symptom	Total	Effect of change of therapy		
		Change for the worse	No change	Improvement
High-dose reverse sequential - after low-dose combination CPA/EE Treatment				
Seborrhoea	19	1	7	11
Acne	25	1	13	11
Hirsutism	38	1	11	26
Alopecia	9	1	3	5
Total	91	4	34	53
Low-dose combination - after high-dose reverse sequential CPA Treatment				
Seborrhoea	5	2	3	-
Acne	11	6	5	-
Hirsutism	14	7	7	-
Alopecia	3	1	2	-
Total	33	16	17	-

Particularly in women in the fifth decade of life, the risk-usefulness relationship must be carefully weighted up in each individual case. Though CPA treatment without oestrogens in menopausal, oophorectomized or hysterectomized women should be considered less problematical from the point of view of side effects, statistical data to confirm this assumption are lacking. CPA treatment is therefore mainly a therapy for women in the third and fourth decades of life.

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