Journal of Steroid Biochemistry, 1975, Vol. 6, pp. 821–826. Pergamon Press. Printed in Great Britain.

ANTIANDROGENS IN THE TREATMENT OF SEXUAL DEVIATIONS OF MEN

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SUMMARY

We report the results of an 8-year clinical investigation of the antiandrogen cyproterone acetate (Androcur, Schering AG Berlin) for the dose-dependent reversible inhibition of sexuality in the human male. The antiandrogen effect is based on the competitive inhibition of all androgens at the androgen sensitive target organs. The selective action at the hypothalamic "mating centres" is the decisive factor for the inhibition of sexuality. The report covers experiences from about 300 men under treatment for a minimum of 2 months and a maximum of 8 years. The orally administered dose of cyproterone acetate ranged from 50–200 mg/day, the intramuscular dose in an oily solution to achieve a prolonged effect from 300–600 mg every week or second week. The dose-dependent reversible effect allows a temporary inhibitory influence on sexuality extending from partial reduction to complete inhibition. This therapy has proved itself to be of real assistance to sexual delinquents and to those who live in constant fear of committing sexual offences. It has proved itself to be a valuable aid in psychotherapy of sexual deviations and perversions in that the perverse cycle is interrupted and a "sexual calm" is created as a starting point for psychotherapy. The interactions of cyproterone acetate with the endocrine system (progestogenic, antigonadotrophic, adrenocortical, testicular interactions) and spermatogenesis are reported.

INTRODUCTION

It is comparatively easy to report on a new possibility of medicinal treatment of a certain disease, as long as the disease being treated is well-defined. But what is a sexual deviation?

The central European limitations of 'normal' sexual behaviour, and hence of sexual deviations, differ from those of other continents. Not infrequently, magazine-educated paedophiles in Europe try to remind us of the accepted procedures in African initiation ceremonies. What is accepted on some beaches is considered elsewhere as an infringement. Finally, more widely varying opinions on certain aspects of sexual behaviour, for example onanism, than those held by sexual researchers and Roman Catholic theologists are difficult to imagine.

However, the situation is not so complex as regards the differences between sexual deviations and sexual perversions. A definition was propounded by Giese[1] as long ago as 1962: Sexual deviations can develop into perversions when a certain behavioural system becomes the exclusive or at least primary system and very specific indicating signs appear:

1. decline into sensuality
2. increasing frequency of sexual activity with decreasing satisfaction
3. development of phantasy, practices and finesse
4. promiscuity and anonymity
5. addiction to the experiencing of sex
6. periodical impulsive unrest, restlessness, nervousness and irritability.

Schindler[2] defines a sexual deviation as a departure from the cultural norm in the choice and/or the form of the stimulating situation which promotes the achievement of an orgasm; also disharmony with this norm in respect of the frequency of sexual activity and avoidance of the orgasm.

A man with a sexual deviation as such does not necessarily require treatment. The particular circumstances dictate the necessity for therapy.

To clarify the situation for the therapeutic aspects we have therefore drawn up a simplified formulation: A sexual deviation which requires treatment is sexual behaviour which deviates from the psycho-physiological initial situation, is punishable and/or causes personal affliction. Punishable sexually deviant behaviour embraces under the collective term of sexual delinquency all actions of legally answerable persons which contravene the norms of criminal law of a particular state or country. Personal affliction can have widely differing causes. It can become unbearable not only in punishable sexually deviant behaviour; scruples about onanism held by sensitive youths with a church-induced neuroticism can sometimes lead as far as suicide. Even an individually permanent, excessive sex drive or sex drive which is considered as disturbing in special situations, for example pregnancy in the wife, constitutes an indication for medical treatment if the resulting affliction causes the person to seek medical aid.

Mode of action

The possibility of a reversible, medicinal, dose-dependent reduction or inhibition of sexuality in men was presented with the synthesis of the steroid cyproterone acetate by Wiechert and co-workers [3] and the animal-experimental demonstration of the antiandrogenic action of this substance by Neumann and co-workers [4].

The trial preparation SH 8,0714, now introduced onto the market under the trade name of Androcur, was supplied to us for testing for this purpose by Schering AG Berlin/Bergkamen, in May, 1966.

The present report covers the experiences from about 300 men under treatment for a minimum of 2 months and a maximum of 8 years.

Antiandrogens inhibit competitively the action of endogenous and exogenous androgens at all androgen target organs. The competitive inhibition of androgen function at the diencephalic androgen sensitive receptors through cyproterone acetate is the decisive site of action for the inhibition of sexuality in men. It induces a reduction in the sexuality of the man in the order libido—ability to erect—orgasm. The reversibility of the effect proceeds in the same order.

Clinical results

Coincidentally with the results of the overall evaluation of the clinical investigation of cyproterone acetate in sexual deviations, in which Mothes and co-workers [5] reported on the treatment of 547 men including about 100 of our patients, we established that, in 80% of cases treated, it was possible to inhibit sexuality to the desired degree with 100 mg Androcur per day *via* the oral route. 20% of the patients required 200 mg orally per day. 50 mg per day proved to be sufficient when, in certain cases, no more than a reduction of sexuality was desired.

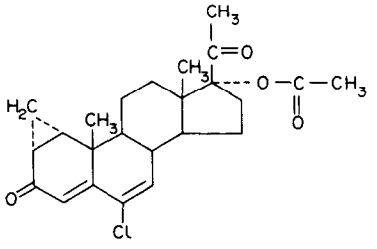

Fig. 1. Cyproterone acetate

In most cases the first signs of Androcur action are reported at the end of the first week of treatment as a reduction of libido and ability to erect. The maximum effect which can be expected with the respective dose is reached by the end of the third week of treatment. This is in accordance with results of Gerhards and co-workers [6] on the biodynamics of cyproterone acetate after oral administration to men.

Oral administration of 100 mg cyproterone acetate daily as simulated on the analog computer is cumulative; an equilibrium in the tissue compartment being reached after 3 weeks. If 200 mg orally is being administered per day, according to the studies of Ott and Hoffet[7] the number of sperm is reduced to less than one million per millilitre after eight to ten weeks of treatment. In many cases at this time a spermiogram control is no longer possible even after oral treatment with 100 mg per day because of the total absence of orgasm. In the differential sperm count immature cells dominate. Städtler[8] demonstrated by testicular biopsy that spermatogenesis is arrested at the spermatocyte level. Spermatids are formed only rarely. When the daily dose was reduced from 100 to 50 mg orally he observed proliferation of the spermatogenic epithelium and also maturation to sperms. In general, however, spermatogenesis was still reduced.

Cyproterone acetate is now available in oily solution for intramuscular administration. In this form it has a depot effect. According to results to date, the injection of 300 to 600 mg cyproterone acetate in oily solution at intervals of 7 to 14 days achieves the same therapeutic result as the oral administration of 100 or 200 mg daily. In each individual case we first of all check the ability of the patient to respond to Androcur by oral administration and then, when the desired therapeutic effect has been reached, we transfer the patient to the parenteral form of administration. The injection treatment makes it possible for an easy check to be made on whether the treatment of delinquents on probation is being carried out reliably, simply by consulting a therapy control card counter-signed by the injecting therapeutist.

Reversibility

The reversibility of the effect proceeds in the same order as the onset of action, that is, libido normalizes first of all, followed by the ability to erect and experience an orgasm and, lastly, spermatogenesis. In all our patients who have been discharged from the therapy, spermatogenesis has returned to normal by the end of the fifth month after withdrawal of Androcur medication.

For pharmacokinetic reasons, however, the reversibility of the effect after termination of parenteral therapy may be delayed. Cyproterone acetate has an affinity for fatty tissue; the depot formation after intramuscular injection can be greater than after oral administration by reason of different absorption conditions; the delayed release from the depots can delay the complete reversibility of the effect [6].

Tolerance, side effects

Tolerance of Androcur is excellent even during long-term treatment. The good liver tolerance merits particular note. General physical condition in about 30% of Androcur patients is somewhat impaired during the 2nd to the 6th week of treatment at the most by easy fatigability, an increased sleep requirement, adynamia and general decreased activity. During this time an increased incidence of depressive mood conditions may be recorded. Concomitant psycho-pathological symptoms, such as disturbed affectivity, inability to concentrate, inner unrest, nervousness and irritability, depressive basic mood or lability of mood and disturbances of drive functions—all associated with the disturbed sexual behaviour—tended to normalize as the therapy progressed. We observed increases in weight, particularly in patients with a carbohydrate-rich diet.

In about 20% of the treated cases and starting at about the 6th to 8th month of treatment, we observed temporary and protracted gynaecomastia. This usually starts with increased sensitivity of the mamillae and rarely exceeds the scale of pubertal gynaecomastia; nutritionally adipose patients develop fat pads in the mammary region, which makes the gynaecomastia appear more pronounced than it actually is. Galactorrhoea of the left breast was observed in only once case. Even in this case the galactorrhoea and gynaecomastia were reversible after termination of medication.

During long-term treatment with Androcur, a decrease of body hair, increase and softening of scalp hair and a decrease in sebum excretion was observed in about 10% of cases. Collaborative studies with Burton and Shuster [9] have shown that the sebum excretion rate in men being treated with cyproterone acetate drops to below the values observed in female controls.

The effect on nitrogen balance during treatment with Androcur was observed with uneasy interest. It appeared that the androgen-related anabolic effect was taking place in the same receptor systems. However, long-term balance studies of nitrogen, calcium and phosphate by van Wayjen and co-workers [10] demonstrated that the initial negative nitrogen, calcium and phosphate balances normalized again after about three months of treatment—probably because of counter-regulatory processes. These clinico-chemical study results are corroborated clinico-empirically by the fact that none of the long-term patients has complained about a reduction of physical performance or vitality generally and radiological examinations have produced no indications of osteoporotic changes.

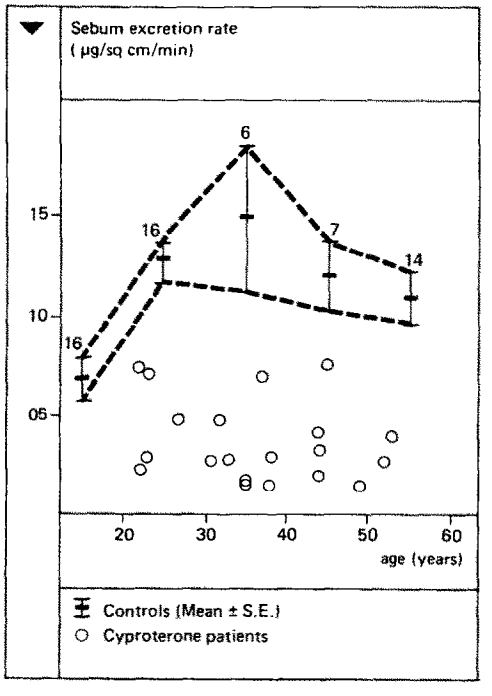

Fig. 2. Sebum excretion rate in men treated with cyproterone acetate.

Contraindications and less suitable cases for treatment

Because of the initially negative nitrogen balance, consumptive diseases must be considered as medical contraindications for treatment with Androcur. Thrombophlebitic and thromboembolic changes and unstabilized diabetics make a very exact assessment of the risk necessary.

Cases which are only suitable for antiandrogen treatment under certain circumstances and which can only be partially, and sometimes not at all, inhibited sexually are patients with posttraumatic, postencephalitic or cerebrosclerotic defects in the region of the hypothalamus in whom the sexual disorder is a result of abnormal excitation processes in the diencephalic androgen receptor areas themselves and is thus androgen-independent.

In some patients with central injuries the partial inhibition of sexuality which can be achieved is sufficient to allow social integration. We hardly need mention that Androcur also has no effect in imbeciles with stereotyped movements reminiscent of masturbation practices or psychotic patients with hallucinations of a sexual character.

Antiandrogens influence only the intensity and not the direction of the sexual drive. With Androcur one can reduce the "wind force" or create a "sexual calm"; the "wind direction" remains basically unchanged. It is, however, obvious that torn sails can be repaired more easily in a calm than in a storm: the "sexual calm", the reduction in the driving force created by Androcur provides more favourable starting conditions for sexual pedagogical or psycho- and sociotherapeutic measures. Thus, if the alteration of a sexually deviant pattern of behaviour is under discussion, the medicinal inhibition of sexuality must be accompanied by psycho-therapeutic treatment—in the widest sense of the term—which is individually adapted to the possibilities [11].

For certain sexual deviations, behaviour therapy can be considered to start as soon as the accustomed sexual reaction fails to occur: our experience has shown that the exhibitionistic variant of masturbation in public is the main one of these. In sufficiently intelligent men the failure of the reaction to occur following protracted visual stimulation appears to lead to a learning or accustoming or experiencing effect which can best be compared with the extinction of a conditioned reflex. Despite the rapid reversibility of the antiandrogen effect, more than 25 of our patients whom we discharged experimentally from the treatment did not revert to the sexual deviation which had led to the therapy. Instead, they developed a sexual life which conforms to the "norms" of our society. None of the 25 patients concerned was awaiting trial or had been placed on probation, so there are no grounds for suspecting that they were merely simulating normalized sexual behaviour in their own interests. These cases have been followed up for between

1 and 5 years. The shortest duration of treatment was eight months.

About 50% of the men whom we have treated with Androcur requested treatment because of a personal affliction. They had no criminal record. Disturbed partner relations with consequences under civil law and beginning or pronounced social disintegration were surmounted in many cases by the antiandrogen treatment. Some of these patients were hovering in the criminological approaches to the criminal law.

The prognosis is unfavourable in men who become conspicuous mainly or exclusively through alcohol disinhibition. It is also unfavourable in all those cases in which the demonstrated deviant behaviour is not accompanied by a proper sexual action or in which the apparently sexually deviant behaviour has become detached from and independent of the actual sexuality, for example, exhibitionists who present non-excited genitalia, that is, they simply exhibit for the sake of exhibiting. In these cases there is no reflex arc, no perverse cycle to be interrupted; and, for example, heterosexually or homosexually paedophilic patients in whom the usually manual manipulations have become independent in a neurotically fixed form and have become detached from the active sexuality of the offender: despite optimal medicinal treatment the manipulations are continued.

Therapeutic spectrum of Androcur

There are limitations to the therapeutic spectrum of Androcur. There is a widely-held but nevertheless erroneous belief that aggression is androgen dependent. That it is not so has been amply demonstrated by all the results so far available. Androcur is therefore not a suitable agent for the breaking-down of aggression or for the treatment of aggressiveness unless the aggression is sex-related.

Androcur is not an agent which can be used for restrictive, repressive-regressive or ecclesiogenic-neurotizing sexual-education. Androcur is not basically indicated in homosexuality; this variant of sexual behaviour only requires treatment when subjective affliction causes the sufferer to seek treatment.

Androcur is not an agent for the reduction of male fertility, for we saw a restitution of spermatogenesis during a long-term-treatment according to the biopsy-results of Städtler and co-workers [8]. There were 3 pregnancies in our study (Tables 1–3).

Interactions with the endocrine system

Pharmacologically, cyproterone acetate belongs first and foremost to the group of antiandrogens, but it also possesses a partial progestational action. Although this partial progestational function has no direct significance for the reversible reduction of sexuality, by reason of the cybernetic regulatory mechanism in the endocrine system it is the vital factor which allows long-term therapy with an antiandrogen [12] (Fig. 3).

Table 1. Cyproterone acetate, 33-year-old man

1 month 100 mg, 21 month 50 mg/day orally
First year: no ejaculate
17th month: 1·9 ml
29 mill. sperms/ml
motility (20') 50%
fructose conc. 2900 μg/ml
abnormal sperms 9%
precursers 6%
Pregnancy, 2nd month

Table 2. Cyproterone acetate, 41-year-old man

10 months 100 mg, 19 months 50 mg/day orally
First year: no ejaculate
21st month: 2 ml
37·8 million sperms/ml
fructose conc. 3100 μg/ml
abnormal sperms 9%
precursers 3%
Girl born at term

The competitive inhibition of the hypothalamic androgensensitive receptors by a "pure" antiandrogen, *i.e.* by an antiandrogen without partial antigonadotrophic action, has the same effect on the production and secretion of gonadotrophin releasers and gonadotrophin release from the pituitary as surgical castration.

With cyproterone acetate the increase in gonadotrophin release, resulting from the antiandrogen action is to a great extent counterbalanced by the antigonadotrophic action of the partial progestogenic function, as assays of gonadotrophin excretion in 24-h-urine, spermatogenic findings and clinical findings during long-term therapy with cyproterone acetate have demonstrated.

In the first months of treatment in all cases examined the antigonadotrophic action from the progestogenic partial action was clearly superior to the increase in gonadotrophin production and secretion rate resulting from the partial antiandrogen action.

In this case (Table 4) the maximal antigonadotrophic effect was registered at the end of the 4th month of treatment. Between the 7th and the 15th month ICSH and TGA excretion recover to the pre-treatment values.

The equalization of the initially dominant antigonadotrophic action occurs at different times depending on the individual and also on the daily dose; when 100 mg orally per day are administered, this usually occurs between the 8th and the 15th month of treatment.

If 200 mg per day of cyproterone acetate are given orally, equalization of the initially dominant antigonadotrophic action seems to take a bit longer. In most cases it occurs between the 15th and the 20th month of treatment (Table 8).

As long as an antigonadotrophic effect is demonstrable, one must expect suppression of spermatogenesis from its presence alone; the occupation of

Table 3. Cyproterone acetate, 27-year-old man

13 months 100 mg/day orally (controlled)
Fertilization during the 13th month of treatment.
Girl born at term

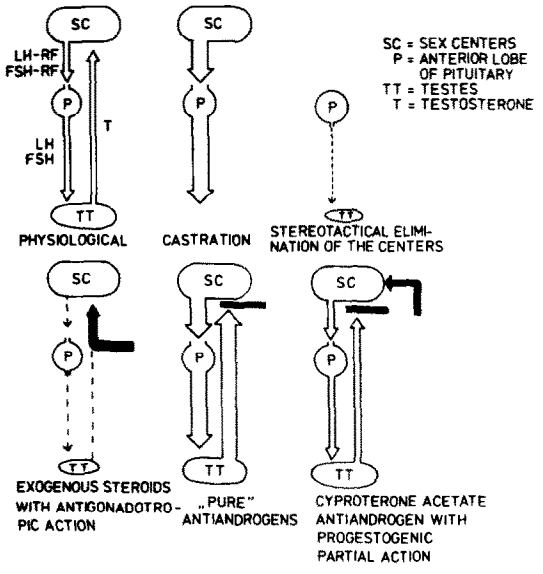

Fig. 3

Table 5. Gonadotrophin excretion during cyproterone acetate treatment with 200 mg/day orally

Gonadotrophins during 200 mg/day Cyproterone acetate treatment (IU 2nd IRP for HMG)	ICSH	TGA*	FSH
Pretreatment	32	18	61
values	36	14	24
months:			
2	<7	11	<15
5	<2·5	9	<12
8	<3	<4	<20
15	5	11	<15
18	20	13	18
23	37	17	31
30	33	31	33
34	43	22	61
48	31	13	72
58	38	34	45

* Total gonadotrophic activity.

the androgen-sensitive testicular receptors is of only secondary importance for the inhibition of fertility during this therapy period.

With the normalization of gonadotrophin production and secretion, Leydig cell function and hence testosterone production and secretion must also normalize. Whilst an antiandrogen is still active, however, a normalization of spermatogenesis or of the ejaculate need not necessarily result. The decisive factor for spermatogenesis is the intratesticular testosterone level but for the ejaculate it is the androgen-dependent excretory function of the accessory sex glands.

The intratesticular testosterone level should normalize with the return of gonadotrophin excretion values to the individual pre-treatment norm. If the daily administered dose of cyproterone acetate allows an adequate excretory function of the accessory sex glands, one can theoretically expect a fertile ejaculate from the moment gonadotrophin secretion normalizes.

It has been demonstrated that the diencephalo-hypophyseal system/adrenal cortex, thyroid, posterior lobe of the pituitary, and the melatonin balance are not influenced by Androcur therapy.

In all cases, our longterm treated patients showed no impairment of adrenocortical function.

The reactivity of the adrenal cortex to ACTH, the oral Metopirone test and ACTH suppression through dexamethasone showed no deviations from the norm in 10 men studied who had been treated with 100 or 200 mg cyproterone acetate orally per day. The treatment periods up to the test varied between 1 and 4 years.

During the eight years of the clinical investigation, antiandrogen treatment with Androcur has shown itself to be effective in the reduction of sexuality in

Table 4. Gonadotrophin excretion during cyproterone acetate treatment with 100 mg/day orally

Gonadotrophins (IU 2nd IRP HMG) Cyproterone acetate treatment 100 mg/day (47 years)	ICSH	Total gonadotrophic activity
Pretreatment	4	3
values	3	3
months:		
2	<3	<3
4	<3	<2
6	<3	2
10	4	3
12	4	2
18	5	7
24	5	5
36	5	6
48	6	4
60	4	3
72	4	4
84	5	3

Table 6. Adrenocortical function during longterm treatment with 100 mg cyproterone acetate orally/day

17-Oxosteroids and 17-oxogenic steroids (mg/24h) Cyproterone acetate treatment 100 mg/day (47 years)	OS	OGS
Pretreatment	10·4	11·4
values	8·2	5·1
months:		
2	13·5	6·5
4	13·3	11·3
6	8·8	5·6
10	16·3	9·1
12	8·6	6·0
18	10·5	9·9
24	13·4	15·9
36	8·7	8·6
48	13·4	9·9
60	11·4	11·7
72	9·0	7·4
84	8·8	9·0

men. Androcur provides new possibilities in the difficult field of the treatment of sexual deviations and perversions in men.

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