REVERSIBLE AZOOSPERMIA INDUCED BY THE ANABOLIC STEROID 19-NORTESTOSTERONE

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Summary Esterified 19-nortestosterone, an anabolic steroid which has been in clinical use for over 20 years, was administered intramuscularly to five healthy volunteers in doses of 100 mg/week for 3 weeks followed by 200 mg/week for a further 10 weeks. Azoospermia occurred 7 to 13 weeks after initiation of treatment and persisted for 4–14 weeks after the last injection. Serum gonadotropin and testosterone levels were reduced, but androgenic effects were maintained as indicated by unchanged libido and potency. No serious side-effects were noted. 19-nortestosterone appears to be a potential agent for male fertility control.

Introduction

DESPITE continuing demand, no reversible chemical method for male fertility control is yet available.[1] One promising possibility is based on the suppression of pituitary gonadotropin secretion by steroids, resulting in testicular atrophy and cessation of spermatogenesis. This suppression can be achieved by progestagens in combination with testosterone, which is required to maintain androgenic effects.[2] However, a satisfactory steroid combination has yet to be found. Testosterone alone may also suppress spermatogenesis and simultaneously maintain androgenic effects. However, probably because the threshold between suppression and stimulation of testicular function by testosterone is narrow,[3] testosterone treatment has failed to give satisfactory male fertility control.[4,5]

As part of a systematic search for a steroid combining androgenic and progestagenic activities we tested 19-nortestosterone, which has been used clinically for over 20 years as an anabolic steroid, with no serious side-effects reported. In addition, it is used by athletes believing that it will promote muscular growth and strength, although controlled studies have demonstrated that anabolic steroids have no effect on muscle development in normal men.[6,7] Despite its long history of application, effects of 19-nortestosterone on the testes remained unknown.

Subjects and Methods

Five healthy men aged 21–25 years consented to participate in the study after receiving extensive information about its aims and risks, in accordance with German drug regulations. None of the subjects had ever had any serious disease. All were active in sports and, aware that they were receiving an anabolic steroid, undertook heavy physical training during the treatment phase. The subjects had stable sexual relations during the investigation.

Physical examination, clinical chemistry, haematology, serum levels of the hormones luteinising hormone (LH), follicle-stimulating hormone (FSH), prolactin, and testosterone, and semen analysis (sperm density, motility, morphology, and seminal fructose) were carried out twice during the control period (A and B): all results were normal. All subjects' spermatozoa were functionally intact as assessed in the heterologous ovum penetration test.[8,9]

The subjects were given intramuscular injections of 19-nortestosterone-hexoxyphenylpropionate (Pharmaleo, Ratingen, West Germany), for the first 3 weeks 100 mg per week, then two 100 mg injections per week for a further 10 weeks. Throughout the study the subjects were examined physically, and body weight and testicle and prostate size (as assessed by orchidometer and rectal palpation, respectively) were recorded. Blood samples for endocrine measurements were taken at the end of every week before administration of the next dose, as well as 1, 4, 8, 16, and 20 weeks after the last injection. Clinical chemistry was repeated in weeks 2, 5, 8, and 11 of treatment and 1, 4, 8, 12, 16, and 20 weeks after treatment. Ejaculates were obtained during weeks 4, 7, 11, 12, and 13 of treatment. All subjects were followed up for 16 weeks. Seminal parameters had then returned to normal in two subjects. The remaining three were followed up to week 24.

Semen evaluation was carried out according to World Health Organisation guidelines.[10] The subjects were requested to abstain from sexual activity for 48 h–7 days before the investigation (48 h in most cases). Testosterone was isolated from serum and separated from 19-nortestosterone by high-performance liquid chromatography, then measured by radioimmunoassay.[11,12] Reagents provided by the WHO Matched Reagents Programme were used for measurement of serum LH by radioimmunoassay. FSH (IRE, Düsseldorf, West Germany) and prolactin (Serono, Freiburg, West Germany) were measured with commercially available radioimmunoassay kits.

All results, expressed as mean±SEM, were analysed by Student's paired *t* test with the means of the two control values (A and B) as points of reference.

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Results

None of the five volunteers complained of any discomfort during the study and there were no effects on general health, no gynaecomastia, and no acne. Prostate size did not change. Libido and potency as reported in weekly interviews were unaltered. Testicular volumes fell from 39±3 ml to 21±3 ml at the end of treatment but returned to the original volume 16 weeks after treatment (fig 1). Body weight (87·5±0·9 kg at the beginning of the study) increased continuously to 94·0±1·9 kg at the end of treatment; 16 weeks after treatment it had fallen to 92±2·6 kg.

In all five volunteers levels of LH, FSH, and testosterone were reduced throughout treatment; prolactin levels were unchanged (fig 2). FSH and LH remained below control levels until 8 and 16 weeks after treatment, respectively, and FSH was significantly above the control level at week 16. Serum testosterone concentrations returned to normal even more slowly, reaching control levels 6 months after the last injection.

Azoospermia was first observed in one subject after 7 weeks' treatment, and by week 13 all five men were azoospermic (fig 3). Azoospermia persisted for 4 to 14 weeks after treatment. However, the volunteer who first became azoospermic had 0·2 million sperm per ml in the first post-treatment week. Seminal measurements had returned to normal 8 weeks after treatment in one subject, 14 weeks in another, and 20 weeks in two. In the fifth subject recovery was slow; 24 weeks after treatment the sperm concentration was still only 1 million/ml. (However, when subject 5 was investigated 30 weeks after treatment, all his seminal parameters had returned to normal: 33 million sperm/ml, 75% motile sperm, 51% normally formed sperm.) Whenever the heterologous ovum penetration test could be done the sperm were classified as functionally normal, except in subject 5 after 11 weeks' treatment, when only 3% of the hamster eggs were penetrated (lower normal limit 10%). Ejaculate volumes and seminal fructose concentrations did not change significantly during the study (fig 1).

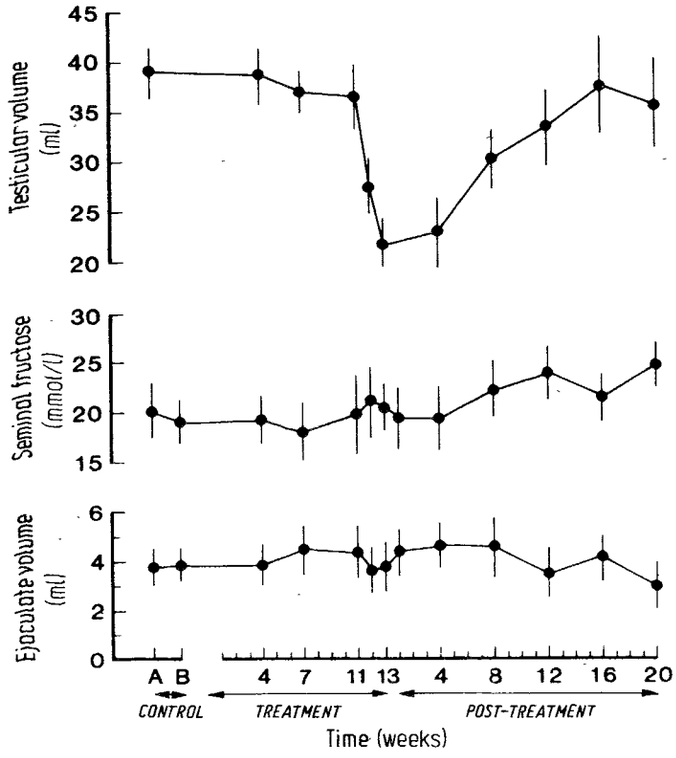

Fig 1—Testicular volume, ejaculate volume, and seminal fructose.

Values at week 20 are derived from only three subjects.

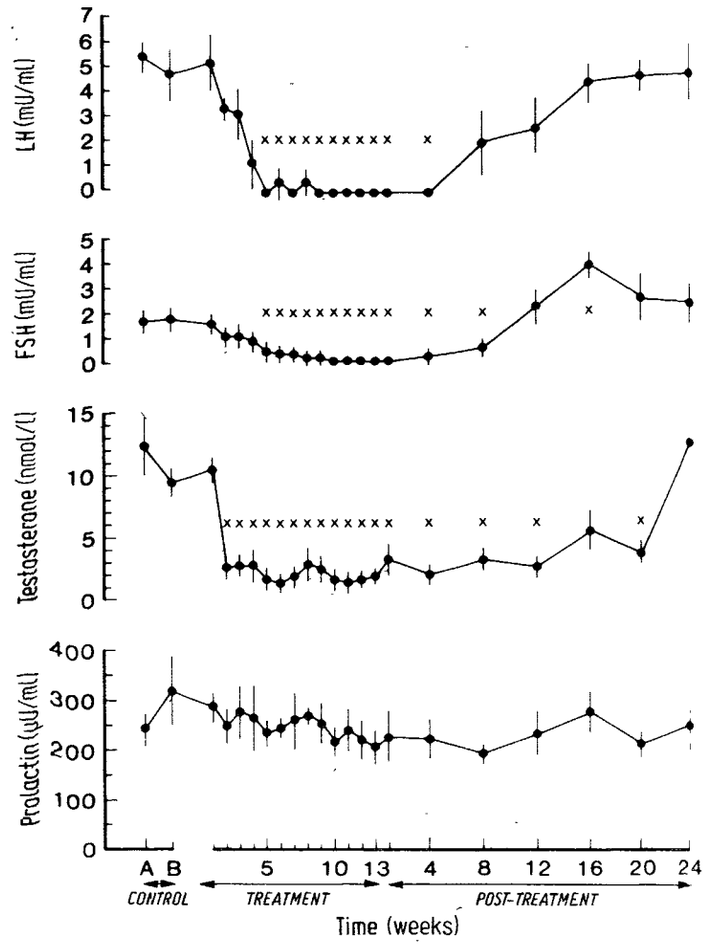

Fig 2—Serum levels of LH, FSH, testosterone, and prolactin.

Values at week 20 are derived from only three subjects. × = significant ($p<0·01$) differences from control values.

Serum levels of alanine and aspartate aminotransferases and lactate dehydrogenase were significantly raised on one or two occasions, whereas γ-glutamyl transpeptidase, alkaline phosphatase, and bilirubin did not rise above control levels (see table). Creatinine was raised on four occasions, but uric acid, cholesterol, and protein did not change significantly. The reticulocyte count slowly increased and reached peak values 4 weeks after the last injection: the highest erythrocyte count, haemoglobin, and haematocrit values occurred in weeks 8 and 12.

Discussion

19-nortestosterone is one of the most widely used anabolic steroids, both in clinical medicine and in athletics. It is surprising that this well-known steroid, which has been used for more than 20 years without reports of serious toxic side-effects, has these drastic effects on spermatogenesis. Possible explanations are that cachectic or convalescent patients receiving this steroid are not likely to be primarily interested in reproduction and that the testicular function of athletes taking the steroids secretly has never been thoroughly investigated. The dosage we tested is somewhat higher than that usually given to patients (50 mg/month to 100 mg/week) but is still lower than the quantities occasionally injected by

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—	Control		Weeks of treatment				Weeks post-treatment					
	A	B	2	5	8	11	1	4	8	12	16	20
Alanine aminotransferase (U/l)	13·0 ±2·6	13·8 ±2·7	17·6 ±1·1	24·6* ±1·9	16·4 ±1·5	24·2 ±3·0	22·0 ±4·4	18·0 ±4·2	18·2 ±2·3	10·8 ±2·0	14·4 ±0·8	12·2 ±1·0
Aspartate aminotransferase (U/l)	19·8 ±3·9	19·0 ±2·9	20·8 ±1·9	29·6 ±3·5	22·0 ±4·4	26·8 ±3·6	30·8* ±3·9	25·2 ±5·7	23·4 ±3·2	14·6 ±2·8	20·3 ±3·3	17·7 ±1·7
Lactate dehydrogenase (U/l)	136 ±4·9	138 ±6·1	162 ±8·8	200* ±8·1	193 ±15	185 ±17	222 ±20	220* ±15	178 ±18	242 ±19	153 ±6·8	151 ±12
γ-glutamyl transpeptidase (U/l)	16·2 ±1·5	11·6 ±0·8	10·0 ±1·1	17·4 ±2·3	11·4 ±1·7	11·8 ±1·8	11·8 ±2·2	13·0 ±1·8	11·2 ±1·8	10·2 ±0·7	12·8 ±1·9	10·0 ±1·3
Alkaline phosphatase (U/l)	153 ±16	155 ±22	148 ±15	168 ±22	144 ±25	175 ±17	158 ±20	177 ±24	164 ±20	166 ±23	179 ±25	166 ±12
Bilirubin (mg/dl)	0·6 ±0·1	0·8 ±0·1	0·5 ±0·0	0·5 ±0·0	0·6 ±0·1	..	0·6 ±0·1	0·6 ±0·1	0·7 ±0·1	0·5 ±0·1	0·8 ±0·1	0·5 ±0·1
Cholesterol (mg/dl)	189 ±34	179 ±17	179 ±17	186 ±19	222 ±34	215 ±23	188 ±20	206 ±20	203 ±16	216 ±26	185 ±16	200 ±25
Protein (g/dl)	8·3 ±0·2	7·3 ±0·1	7·6 ±0·3	7·5 ±0·2	8·0 ±0·1	7·1 ±0·3	7·5 ±0·3	7·1 ±0·2	7·7 ±0·3	8·1 ±0·2	7·1 ±0·3	6·9 ±0·2
Creatinine (mg/dl)	1·0 ±0·1	1·1 ±0·0	1·2* ±0·1	1·1 ±0·1	1·4* ±0·1	1·3* ±0·1	1·2* ±0·0	1·1 ±0·1	1·1 ±0·1	1·2 ±0·0	1·1 ±0·0	1·2 ±0·0
Uric acid (mg/dl)	4·1 ±0·7	5·3 ±0·4	5·0 ±0·6	3·6 ±0·6	4·9 ±0·6	4·1 ±0·3	3·4 ±0·7	4·2 ±0·3	4·0 ±0·4	3·7 ±0·4	3·7 ±0·3	4·2 ±0·5
Haemoglobin (g/dl)	16·2 ±0·6	16·1 ±0·4	16·8 ±0·5	17·2 ±0·4	17·2 ±0·4	16·5 ±0·5	17·1 ±0·6	16·7 ±0·4	16·9 ±0·5	18·9 ±0·5	17·4 ±0·5	16·7 ±0·6
Haematocrit (%)	44·3 ±0·8	44·3 ±1·0	44·7 ±1·0	46·4 ±0·8	46·8 ±1·4	44·8 ±1·2	48·0 ±1·1	44·0 ±1·1	46·9 ±1·0	51·3 ±1·6	47·9 ±0·6	45·5 ±1·6
RBC ($\times 10^6/\mu l$)	5·2 ±0·2	5·1 ±0·1	5·3 ±0·1	5·5 ±0·1	5·4 ±0·2	5·3 ±0·2	5·6 ±0·2	5·3 ±0·2	5·4 ±0·1	5·9 ±0·2	5·4 ±0·2	5·1 ±0·1
Reticulocytes ($\times 10^3/\mu l$)	4·8 ±0·9	..	3·8 ±0·6	5·8 ±0·7	7·8 ±0·8	14·0 ±2·1	7·6 ±1·4	16·6 ±4·9	13·2 ±2·3	5·8 ±1·6	8·8 ±0·2	9·2 ±1·8
Thrombocytes ($\times 10^3/\mu l$)	177 ±9·2	..	161 ±18	173 ±15	183 ±25	..	169 ±16	176 ±21	167 ±18	168 ±25	187 ±21	173 ±20
WBC ($\times 10^3/\mu l$)	6180 ±400	5380 ±398	6000 ±339	6560 ±575	7000 ±302	5660 ±746	6440 ±458	6160 ±322	6120 ±354	5720 ±338	4733 ±467	5740 ±477

Data as mean±SEM. RBC=red blood cells; WBC=white blood cells. *Significantly different from control values ($p<0·01$).

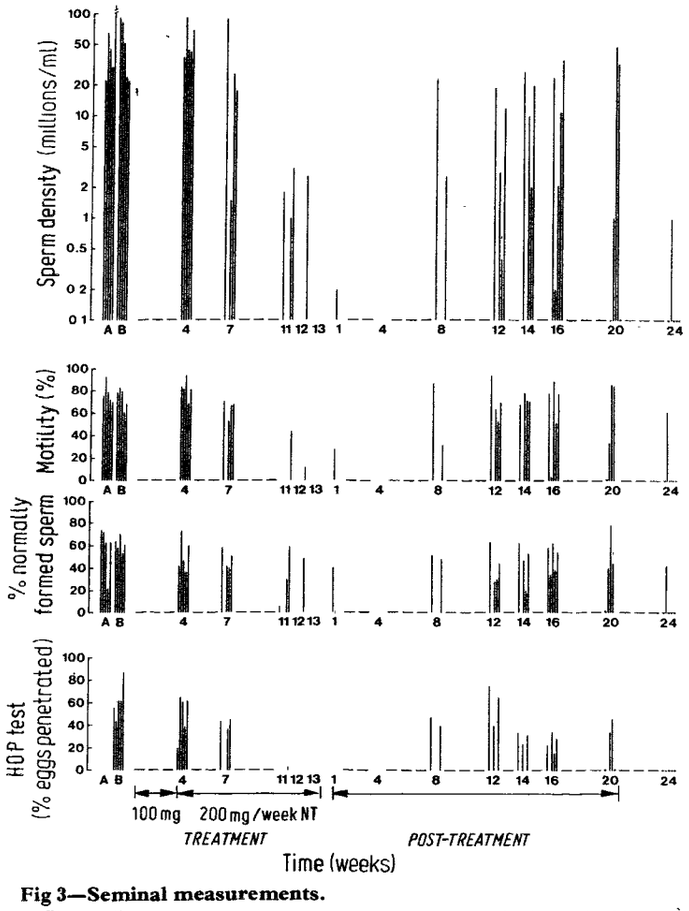

Fig 3—Seminal measurements.

Dots indicate azoospermic semen samples. Open circles in weeks 20 and 24 indicate that semen specimens from these subjects were not investigated, since measurements had returned to normal earlier. HOP test = heterologous ovum penetration test: could not be done if ejaculate contained <1 million sperm.

athletes on the assumption that the drug will improve performance in competition.

After 7–12 weeks' treatment up to 4–14 weeks after the end of treatment the subjects could be considered infertile. The periods of azoospermia lasted for 5–20 weeks; if the sperm concentration of 0·2 million/ml in one subject in the first post-treatment week is disregarded. The suppression of spermatogenesis is apparently caused by suppression of pituitary gonadotropin secretion. In contrast to Bijlsma et al,[13] who described a fall in FSH and testosterone but not LH with 19-nortestosterone, we found simultaneous falls in LH, FSH, and testosterone.

Despite reduced testosterone levels none of our subjects reported a loss of libido or potency. This observation, together with the fact that prostate size, ejaculate volume, and seminal fructose levels did not change, indicates that 19-nortestosterone given in such doses has sufficiently high androgenic potency. In contrast, neither prostate hypertrophy nor acne, which would be expected with a similar testosterone dosage, developed. Therefore, the androgenic properties of 19-nortestosterone seem to be lower than those of testosterone. 19-nortestosterone itself does not bind to oestrogen receptors[14] and is poorly converted to oestrogens. These facts may account for the lack of acne and gynaecomastia in our subjects.

The long-lasting suppression of serum LH, FSH, and testosterone after treatment indicates that 19-nortestosterone must remain in the body for some time. This finding may also explain why recovery of seminal parameters, at least in one subject, was very slow. However, the observation of an extended recovery phase is not uncommon in clinical trials of male fertility control based on steroid treatment.[15]

Testicular size decreased by 50% under treatment, lagging behind the fall in sperm count. None of the subjects nor their

sexual partners noticed the reduction in testicular size and none was informed about it to avoid psychological complications. This unrecognised effect cannot be considered an impeding side-effect.

The erythropoietic effect seen at the end of the treatment phase was expected, since androgens and especially their 5β-metabolites stimulate erythropoiesis.[16,17] 17-methyl-19-nortestosterone[18] and 17-ethyl-19-nortestosterone[19] are hepatotoxic, owing to 17-alkylation, but such effects have not been reported for 19-nortestosterone. The increase in aminotransferase levels may be of muscular rather than hepatic origin, since the volunteers took heavy physical exercise during treatment and γ-glutamyl transpeptidase, alkaline phosphatase, and bilirubin levels did not increase.

The gain in body weight was apparently due to the muscular exercise rather than to an anabolic effect of 19-nortestosterone, since in normal men physical exercise increases muscle mass, regardless of whether an anabolic steroid has been administered.[6,7]

Testosterone or progestagens given as single entities fail to give effective and acceptable male fertility control;[4,5,20] however, the combination of testosterone with progestagens or danazol appears more favourable.[21,22] 19-nortestosterone, an effective androgen but approximately ten times more progestagenic than testosterone,[14] has the qualities of an androgen and a progestagen in a single molecule. Difficulties resulting from the different pharmacokinetics of two steroids given in combination and mutual interference are avoided when 19-nortestosterone is given alone. The effectiveness of 19-nortestosterone in suppressing spermatogenesis and simultaneously maintaining androgenic effects, as well as the long history of this drug uneventful in terms of toxic side-effects, render it an interesting candidate for further evaluation as an agent for male fertility control.

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A SOLUTION TO THE GENETIC AND ENVIRONMENTAL PUZZLES OF INSULIN-DEPENDENT DIABETES MELLITUS

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Summary Studies of the segregation of heterozygous immunoglobulin allotypes in families with several cases of insulin-dependent diabetes mellitus (IDDM) show that germline heavy-chain V (variable region) genes are not major genetic determinants for IDDM, but data for IDDM and Graves' disease together suggest involvement of κ light-chain V genes. Absence of IDDM at birth, the semi-random age of onset, and the 50% discordance of identical twins suggest that somatic mutation of germline V genes is involved in the development of the pathogenetic anti-beta-cell clones. The effect of histocompatibility and other alloantigens on the prevalence of IDDM is readily accounted for by the effect of the "holes" they induce, by natural tolerance, in the immune response repertoire; these alterations apparently affect the chance of emergence of anti-beta-cell clones by the somatic mutations and network of interclonal deletions that constantly change the fringes of the repertoire. Histocompatibility antigens can also influence repertoire development by changing the specificity of conjoint presentation of foreign antigens by macrophages. Antigenic stimulation by particular environmental microorganisms is probably essential to the repertoire development necessary for the occurrence of IDDM. Additionally, beta-cell damage by local infection may play a part by facilitating autoantigen presentation to the immune system.

Introduction

GREAT mystery is made of the interplay of environmental and genetic factors in the pathogenesis of insulin-dependent diabetes mellitus (IDDM).[1,2] Yet a comprehensive explanation is provided by two simple theories—Burnet's forbidden clone theory[3] and the H gene theory.[4] Before recapitulating these theories in the context of IDDM, it is

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