

Drug-Induced Hyperandrogenism

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SUMMARY

Many drugs can induce hyperandrogenic symptoms, such as hirsutism, acne, seborrheic dermatitis, male-pattern baldness, menstrual irregularities, clitoral hypertrophy, or deepening of voice. Anabolic-androgenic steroids, synthetic progestins, and antiepileptics are the most frequently implicated drugs in hyperandrogenism. The mechanisms of androgen excess are various: (1) intrinsic androgenic activity of the drug, (2) interaction with sex hormone-binding globulin, or (3) functional alterations of the hypothalamic–pituitary–ovary axis. Nevertheless, the physiology of these drugs remains generally unclear. Such is the case for valproate, which seems to induce a form of polycystic ovary syndrome (PCOS) by increasing ovarian androgen synthesis. It should be remembered that it is always necessary to rule out other causes of androgen excess, especially an ovarian or adrenal tumor or PCOS, before attributing the symptom(s) to a drug.

Key Words: Hyperandrogenism; hypertrichosis; alopecia; anabolic-androgenic steroids; doping; synthetic progestins; valproic acid.

1. INTRODUCTION

Administration of drugs can induce hyperandrogenic symptoms, including hirsutism, acne, seborrheic dermatitis, male-pattern baldness, menstrual irregularities, clitoral hypertrophy, or deepening of voice. The principal mechanisms resulting in hyperandrogenism are either an increase in circulating androgen levels or an intrinsic androgenic activity of the drug. The drugs most commonly responsible for the development of virilizing effects include anabolic steroids, progestins, and antiepileptics. In addition, the use or abuse of androgens such as testosterone, androstenedione, or dehydroepiandrosterone (DHEA) for improving athletic performance or treating menopausal- or androgen deficiency- (e.g., hyposexuality) related symptoms may result in the development of frank hyperandrogenism.

2. BACKGROUND

2.1. Mechanisms of Drug-Induced Androgen Excess

In addition to the direct contribution of androgens (testosterone, androstenedione, DHEA) use/abuse to increased circulating androgen levels, several mechanisms, which may be associated and operate simultaneously, can explain clinical and biological drug-induced androgen excess. Nevertheless, the physiological mechanisms of this effect sometimes remain unclear.

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Table 1
Selected Androgenic Anabolic Steroids

Androisoxazole	Methyltestosterone
Androstanolone	Metribolone
Bolandiol	Mibolerone
Bolasterone	Nandrolone
Boldenone	Norboletone
Bolenol	Norclostebol
Bolmantalate	Norethandrolone
Chlordrolone	Oxabolone
Cloxostosterone	Oxandrolone
Dehydrochlormethyltestosterone	Oxymesterone
Drostanolone	Oxymetholone
Ethylestrenol	Penmesterol
Fluoxymesterone	Propetandrol
Formebolone	Quinbolone
Furazabol	Silandrone
Mebolazine	Stanozolol
Mesabolone	Clostebol
Mestanolone	Stenbolone
Mesterolone	Testoslactone
Metandienone	Testosterone
Metenolone	Tibolone
Methandriol	Tiomesterone
Methylandrostandiol	Trenbolone
Testolactone	Zeranol

2.1.1. Intrinsic Androgenic Activity of the Drug

Anabolic-androgenic steroids (AASs) (Table 1) and progestins are often synthetic derivatives of testosterone. As such, they may bind to the androgen receptor and exert direct androgenic action. Because the androgen receptor mediates both the anabolic and androgenic actions, no anabolic steroid is devoid of androgenic properties.

2.1.2. Interactions with Sex Hormone-Binding Globulin

Progestins and AASs decrease sex hormone-binding globulin (SHBG) plasma concentration, and thereby increase free testosterone level, by suppressing the hepatic synthesis of SHBG in a dose-dependent manner (1). They may also bind to SHBG, thereby displacing testosterone and increasing the plasma level of free active testosterone. In addition, drugs that induce obesity and hyperinsulinism, such as valproate, indirectly decrease the plasma concentration of SHBG through the negative effect of insulin on SHBG hepatic synthesis. Therefore, an increased concentration of free testosterone explains, at least in part, the high prevalence of hirsutism in women taking these drugs.

2.1.3. Functional Alterations of the Hypothalamic–Pituitary–Ovarian Axis

Some investigators have suggested that valproate and other antiepileptic drugs may interfere with the hypothalamic control of the hypothalamic–pituitary–ovarian (HPO) axis by altering luteinizing hormone secretion through mechanisms involving γ -aminobutyric acid-ergic neurotransmission. Nevertheless, others have suggested that epileptic or psychotic problems themselves may induce these abnormalities.

2.1.4. Increased Endogenous Androgens

By inducing excessive adrenal androgen secretion, chronic treatment with adrenocorticotrophic hormone (Cortrosyn[®] or Synacten[®]) or metyrapone may cause mild hyperandrogenism in women

through peripheral transformation of adrenal androgens to testosterone and dihydrotestosterone. The increase in serum prolactin concentration may in part explain the hirsutism induced by phenothiazines. Indeed, prolactin is thought to increase the concentration of adrenal androgens, notably the metabolite dehydroepiandrosterone sulfate, and to decrease the concentration of SHBG, thereby raising the concentration of free testosterone.

2.2. Anabolic-Androgenic Steroids

AASs are obtained after several chemical modifications of testosterone, which increase the therapeutic index (i.e., the anabolic:androgenic activity ratio): (1) alkylation at the 17 α position (which decreases strongly the hepatic metabolism of the hormone), (2) reduction of C-1,2 binding (which decreases the androgenic activity), halogenation at the C-4 and C-9 positions, (3) esterification of the 17 β -hydroxyl group (which prolongs their duration of action and increases their solubility in the fatty vehicles used for injection), and (4) modifications in the ring structure of the steroid, demethylation at C-19 position (which increases the anabolic action). Most agents contain a combination of these structural changes (Table 1). Oral, parenteral, transdermal, or nasal administration of AASs is possible.

2.2.1. AASs in Sport and Fitness

For the past 50 years, AASs have been used by a wide variety of competitive athletes (bodybuilders, weightlifters, field athletes, swimmers, runners, etc.) with the hope of improving their training, endurance, and performance. A significant number of recreational athletes also seem to be using these drugs. And more and more nonathletes are also abusing AASs with the hope of improving their physical appearance.

The frequency and severity of androgenic effects of AASs depend on the dose, the method of use, the duration of administration, individual differences in susceptibility, and the properties of the molecule (the anabolic:androgenic activity ratio varies between 30:1 and 100:1). Athletes often take more than one steroid at the same time and use dosages that sometimes exceed physiological replacement levels by 10–100 times or even more. The early side effects in women are acne, oily hair and skin, seborrheic dermatitis, hirsutism, and menstrual irregularities. These clinical abnormalities can subside if AAS use is discontinued. With prolonged treatment deepening of the voice, shrinkage of the breasts, male-pattern baldness, and hypertrophy of the clitoris develop and are generally irreversible after discontinuation of AAS use. In adolescents, premature halting of growth has been described (2). The detection of AAS abuse requires specific procedures, which allow for the measurement of the derivative itself.

2.2.2. Other Uses of AASs

With the exception of their use in male hypogonadism treatment, anabolic steroids have been used in a variety of clinical situations with the hope that the beneficial actions would outweigh the risk of androgenic side effects (3). Although androgens increase the production of erythropoietin in the kidney, their efficiency in the treatment of bone marrow failure resulting from aplastic anemia or myelofibrosis or anemia as a result of renal failure is still uncertain.

Danazol is a steroid molecule designed for the treatment of endometriosis. It is more infrequently used because of its androgenic side effects (facial acne and acne of the back, hirsutism, hypertrophy of the clitoris, hair loss, deepening of the voice, weight gain, alterations in lipid metabolism) (4). These manifestations appear early, are dose-dependent, and decrease with discontinuation of treatment. Gonadotropin-releasing hormone analogs, which are equally effective in treating endometriosis, are now more widely used (5,6).

The use of AAS, such as stanozolol and danazol, has been proven successful for the treatment of lipodermatosclerosis, cryofibrogenemia, and secondary Raynaud's phenomenon, probably via fibrinolytic properties. Oral AAS alkylated in the C-17 position increase the level of the serum inhibitor of the activated first component of complement, which is deficient in hereditary angioneurotic edema. Low doses are required, and thus, no serious adverse effects are generally seen (7).

Defective secretion of androgens has been suggested as a component of growth failure in patients with Turner's syndrome. Oxandrolone in combination with growth hormone has been shown to result in growth acceleration and to improve final adult height in these patients without serious side effects (8).

2.3. Synthetic Progestins

Progestins contained in oral second-generation contraceptive agents are 19-nortestosterone derivatives with attenuated androgenic properties. Norsteroids are classified in two main groups: the estranes group, which includes norethisterone (the main active molecule), norethisterone acetate, norgestrienone, lynestrenone, and ethynodiol diacetate, and the gonanes group, which includes norgestrel, levonorgestrel, and 3-cetodesogestrel.

The androgenic activity of progestins is based on two mechanisms. First, the strong similarities in structure between norsteroids and testosterone explain their ability to bind the androgen receptor, inducing directly androgenic effects. Second, progestins lower SHBG and bind to it, thus displacing testosterone and increasing levels of free active testosterone. The androgenic effects are dose-dependent and are variable according to the characteristics of each synthetic progestin.

Few women are affected by hyperandrogenism when using current oral contraceptive pills (OCPs) because of their ethynilestradiol content, which attenuates the androgenic effects of the progestins. In fact, most OCPs are able to reduce circulating free testosterone levels and ameliorate acne and hirsutism. The most frequent symptoms are acne and weight gain, whereas hirsutism is quite uncommon. The exception is progestin-only contraceptives, which tend to cause a higher prevalence of androgenic side effects. Thus, it is essential to exclude an endogenous source of androgens in case of hyperandrogenic manifestations occurring when taking an OCP. New third-generation OCPs containing 19-norpregnane progestins (e.g., gestodene, desogestrel, and norgestimate) have fewer androgenic side effects and are increasingly being used.

2.4. Antiepileptic Drugs

Epidemiological studies have reported that reproductive endocrine disorders, in particular polycystic ovary syndrome (PCOS) and hyperandrogenemia, are more common in women with epilepsy than in normal women. These disorders have been attributed to epilepsy for a long time. More recently it has been suggested that antiepileptic drugs themselves, particularly valproic acid or valproate (VPA), may be directly involved. Valproic acid is a short-chained fatty acid that is commonly used to treat epilepsy (both partial and generalized seizures), bipolar disorders, and migraines. Long-term treatment of women with VPA has been reported to be associated with reproductive disturbances. Moreover, an increased prevalence of clinical and biological hyperandrogenism, hyperinsulinism, and ultrasound criteria of PCOS has been observed in women taking prolonged VPA treatment, but the direct responsibility of VPA is still debated (9,10).

Animal studies examining the effect of long-term VPA treatment have yielded variable results. In the rat, prolonged VPA treatment results in the formation of ovarian follicular cysts and a reduced number of corpora lutea; however, it decreases androgen and progesterone biosynthesis. In isolated porcine follicles, studies showed that overall androgen production is decreased in response to VPA. However, an increase in the testosterone:estrogen ratio resulting from a decrease in granulosa cell aromatase activity was observed. Finally, therapeutic exposure to VPA for a long period (12–15 months) does not reproduce the hormonal or morphological abnormalities of PCOS in nonepileptic, normally cycling rhesus monkeys (11). The discrepancy between these animal and in vitro studies and human data remains so far unexplained.

A number of physiopathological mechanisms have been proposed to account for the reproductive effects of antiepileptic drugs.

2.4.1. Effect on Weight and/or Insulin Resistance

First, significant weight gain is commonly observed with VPA treatment, and it can be associated with the development of metabolic abnormalities, especially insulin resistance. So far the mechanism

Table 2
Drugs or Drug Classes Inducing Generalized Hypertrichosis

Acetazolamide
Calcium channel blockers
Cyclosporin
Diazoxide
Erythropoietin
Hydantoin
Glucocorticoids
Minoxidil
Penicillamine
Psoralens
Retinoic acid
Streptomycin

by which VPA induces such metabolic abnormalities is unknown. However, in a number of cases, reproductive disorders have been observed in patients using VPA in the absence of excessive body weight gain (12). Thus, it seems that the weight gain caused by therapeutic exposure to VPA by itself cannot always explain the reproductive abnormalities observed.

2.4.2. Direct Effect on Ovarian Androgen Production

In vitro experiments have noted a direct effect of VPA on androgen biosynthesis. Indeed, human ovarian theca cells isolated from follicles of both normally cycling and PCOS women have the capacity to respond to a therapeutically relevant concentration of VPA with an increase in androgen biosynthesis. This finding suggests that VPA treatment could independently induce PCOS symptoms in the absence of genetic predisposition. The observation that PCOS theca cells respond more strongly to VPA than normal cells suggests that VPA treatment can further increase androgen synthesis in patients with PCOS. The intracellular mechanisms by which VPA induces a PCOS-like phenotype in these normal ovarian cells have been examined, and an increase in CYP17 and CYP11A, responsible for the expression of production of DHEA sulfate and androstenedione, has been observed. VPA-dependent changes in steroid biosynthesis may result from a modification of chromatin structure, enhancing transcription of genes encoding steroidogenic enzymes (13).

According to these data, it appears that VPA could increase ovarian androgen biosynthesis directly, rather than through an alteration in hypothalamic pituitary function. Nevertheless, the occurrence of PCOS in women treated by VPA probably also depends on additional factors such as frequency and type of seizures, duration of epilepsy, age at onset of seizures, ethnic and genetic predispositions to PCOS, or environmental characteristics.

2.5. Androgen-Independent Drug-Induced Hair Growth or Loss

Drug-induced hypertrichosis must be differentiated from hirsutism because it is independent of androgen stimulation. It describes the growth of terminal and/or vellus hair on areas of the body where the hair is usually short. It depends on the drug dosage and is reversible after drug withdrawal. A large number of drugs may induce this phenomenon, through several mechanisms (Table 2) (14).

The hair growth-promoting action of cyclosporine is partially attributable to its growth-promoting influence on hair epithelial cells caused by a decrease in protein kinase C. It stimulates telogen follicles to reenter anagen. Hirsutism and hypertrichosis could occur simultaneously with cyclosporine treatment. Benoxaprofen induces an abnormal prolongation of anagen growth. Antihypertensive agents that affect potassium channels also affect hair growth. Erythropoietin decreases the inhibiting effect of cortisol on hair follicular activity by lowering its level. Minoxidil is a treatment for male-pattern baldness: when directly applied to the balding scalp, it induces androgen-independent hair growth. Diazoxide and psoralens also often induce hypertrichosis (14). Phenytoin therapy is known to induce a generalized increase in hair growth.

Table 3
Drugs or Drug Classes Inducing Hair Loss

Pro-androgen action
Oral contraceptive pill, danazol, testosterone, anabolic steroids
Antithyroid action
Propylthiouracils, carbimazole, amiodarone, lithium
Prothyroid action
Thyroxine
Lichenoid cicatricial alopecia
Chloroquine, mepacrine, proguanil
Telogen effluvium
Albendazol, allopurinol, amphetamine, boric acid, bromocriptine, captopril, cimetidine, colchicine, coumarins, enalapril, glibenclamide, gold, heparin, heparinoids, hypolipidemic agents (clofibrate, triparanol), indandiones, interferons, levodopa, methyl dopa, methysergide, metoprolol, penicillamine, phenytoin, propranolol, retinol, sulphasalazine
Anagen effluvium
Radiation, cyclophosphamide, doxorubicin, colchicine (high dose), thallium, mercury, arsenic, cantharadin, azathioprine, methotrexate

Alternatively, drugs can induce alopecia through loss of either anagen or telogen hairs (Table 3). Anagen hair loss is usually dramatic, inducing an abrupt cessation of mitotic activity in rapidly dividing hair matrix cells. Telogen effluvium (shedding of telogen or dead hairs) induces premature rest of the follicle.

3. CONCLUSION AND FUTURE AVENUES OF INVESTIGATION

The diagnosis of drug-induced androgen excess is often evident except in the case of illegal administration of anabolic androgenic steroids. However, other etiologies of hyperandrogenism should not be ignored, particularly an androgen-secreting tumor or PCOS (which may also be induced or worsened by certain drugs). Our knowledge of the physiological mechanisms underlying drug-induced hyperandrogenism continues to develop, particularly concerning VPA. Indeed, this common antiepileptic drug has been suggested to induce a PCOS-like phenotype. The role of the weight gain often associated with VPA treatment in the development of reproductive disturbances is still unclear. Further investigations are required to elucidate the mechanism underlying the interaction between VPA and ovarian theca cells. These studies have the potential for improving our understanding of the mechanisms underlying ovarian hyperandrogenism in PCOS, because this molecule induces alteration of ovarian steroidogenic enzyme activity that mimic those observed in spontaneously occurring PCOS (*see* Chapter 18). Investigative efforts should also be turned to designing newer antiepileptic drugs devoid of hyperandrogenic and reproductive side effects.

KEY POINTS

- Intrinsic androgenic activity of the drug, interactions with SHBG, or alterations of the HPO axis are the main mechanisms of drug-induced hyperandrogenism. Nevertheless, for some drugs, the mechanism(s) of hyperandrogenism remain unclear.

- The androgenic side effects of AASs depend on the dose, duration of administration, properties of the molecule (i.e., the anabolic:androgenic activity ratio), and individual differences in susceptibility; with intensive and prolonged use, side effects may become irreversible, even with discontinuation.
- Unlike oral second-generation contraceptive agents, new third-generation OCPs contain progestins with few androgenic effects.
- Valproic acid appears to stimulate increased ovarian androgen biosynthesis, which appears to be independent of the metabolic changes induced by this antiepileptic drug.
- In the case of severe symptoms in a woman taking a drug known to induce hyperandrogenism, other etiologies should be considered, particularly an androgen-secreting ovarian or adrenal neoplasm or PCOS.

REFERENCES

1. Song S, Chen J, Lu C, et al. Effects of different doses of norethisterone on ovarian function, serum sex hormone binding globulin and high density lipoprotein-cholesterol. *Contraception* 1993;47:527–537.
2. Rogol A, Yesalis CE. Anabolic-androgenic steroids and the adolescent. *Pediatr Ann* 1992;21:175–188.
3. Wilson JD, Griffin JE. Progress in endocrinology and metabolism: the use and misuse of androgens. *Metabolism* 1980;29:1278–1295.
4. Barbieri RL, Evans S, Kistner RW. Danazol in the treatment of endometriosis: analysis of 100 cases with a 4 year follow-up. *Fertil Steril* 1982;37:737–746.
5. Cirkel U, Ochs H, Schneider HPG. A randomized, comparative trial of triptorelin depot (D-Trp-LHRH) and danazol in the treatment of endometriosis. *Eur J Obstet Gynecol* 1995;59:61–69.
6. Wright S, Valdes CT, Dunn RC, Franklin RR. Short-term Lupron or danazol therapy for pelvic endometriosis. *Fertil Steril* 1995;63:504–507.
7. Elfman T, Falanga V. Stanzolol as a novel therapeutic agent in dermatology. *J Am Acad Dermatol* 1995;33:254–258.
8. Nilsson KO, Albertsson-Wikland K, Alm J, et al. Improved final height in girls with Turner's syndrome treated with growth hormone and oxandrolone. *J Clin Endocrinol Metab* 1996;81:635–640.
9. Isojarvi JI, Laatikainen TJ, Pakarinen AJ, Juntunen KT, Myllyla VV. Polycystic ovaries and hyperandrogenism in women taking valproate for epilepsy. *N Engl J Med* 1993;329:1383–1388.
10. Verrotti A, Greco R, Latini G, Chiarelli F. Endocrine and metabolic changes in epileptic patients receiving valproic acid. *J Pediatr Endocr Metab* 2005;18:423–430.
11. Ferin M, Morrell M, Xiao E, et al. Endocrine and metabolic responses to long-term monotherapy with the antiepileptic drug valproate in the normally cycling rhesus monkey. *J Clin Endocrinol Metab* 2003;88:2908–2915.
12. Bilo L, Meo R, Valentino R, Di Carlo C, Striano S, Nappi C. Characterization of reproductive endocrine disorders in women with epilepsy. *J Clin Endocrinol Metab* 2001;86:2950–2956.
13. Nelson-DeGrave V, Wickenheisser J, Cockrell J, et al. Valproate potentiates androgen biosynthesis in human ovarian theca cells. *Endocrinology* 2003;145:799–808.
14. Australasian Hair and Wool Research Society's website: <http://www.alopecia.com>