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Finasteride adverse effects and post-finasteride syndrome; implications for dentists

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Finasteride adverse effects and post-finasteride syndrome; implications for dentists

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Abstract

Finasteride is a 5 α -reductase inhibitor widely used in present in the therapeutic approach of androgenic alopecia. Adverse effects consist in variable sign and symptoms, the most common being represented by mental troubles (reduced feeling of life pleasure or emotions, depression), physical impairments (loss of muscle tone and/or mass) and sexual complains (loss of libido and sexual potency). An increasing number of studies identify and describe even a post-finasteride syndrome (persistent adverse affects three months or more after finasteride cessation) or new adverse effects including but not limited at the skin level or oral cavity (marginal periodontium).

We intend to present in this study several oral adverse effects encountered during finasteride administration, represented by mild and moderate signs which generally responded to topical procedures without to require the stop of the drug administration. New studies on large samples will further document the existing relation between the described oral adverse effects and the implied pathophysiological mechanisms. For this moment, we are taking into account as possible mechanisms- a direct action of finasteride administration, possible indirect consequences due to hormonal interferences, or coexisting factors with finasteride administration that were not detected.

Keywords: finasteride, oral side effects, post-finasteride syndrome



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Introduction

Finasteride is a 5 α -reductase inhibitor, extensively used in present in the therapeutic approach of male pattern hair loss. It is approved only for men with androgenetic alopecia, being not indicated for women or in the case of pediatric patients. Finasteride is also used for benign prostatic hyperplasia (5mg/ day), being suspected that could increase the risk of high-grade prostate cancer. In respect to androgenetic alopecia, finasteride can be administered in the form of tablets, 1mg/ day, or as topical solution applied on the scalp once or twice a day (1-3).

Finasteride is extensively degraded to inactive metabolites in liver, which are further eliminated through urine and bile. As active compound, finasteride prevents conversion of testosterone, progesterone and deoxycorticosterone to the corresponding metabolites, namely dihydrotestosterone (DHT), dihydroprogesterone, dihydrodeoxycorticosterone. All these mediators act within the brain modulating not only sexual receptors but also the action of γ -aminobutyric acid on the corresponding GABA receptors. Accordingly, the most frequent adverse effects induced by finasteride are related to mental (depression) and sexual (loss of libido and sexual potency) symptoms, which are encountered not only during finasteride administration but also after treatment cessation (as post-finasteride syndrome) (4, 5).

Recent studies show that finasteride side effects can occur at the level of oral cavity too, in the form of various signs and symptoms (erythema, purpura, gingival hypertrophy) (6, 7). The current study is aimed to present oral finasteride adverse effects encountered on a sample of men taking the drug for androgenic alopecia.

Materials and Methods

The study group taking finasteride was represented by eighty four subjects with androgenic alopecia, who received the drug 1 mg daily, six month or more. Inclusion criteria used to recruit subjects were as follow: men with androgenic alopecia, presenting no significant (mental, sexual, cutaneous, oral) affections prior the treatment, and taking no specific diets or drugs for general conditions (obesity, hypertension, etc.). According to literature data, finasteride proved to be able to induce a lot of adverse effects during and after administration. As a consequence, we designed and performed the study with several specialists to cover a wider field of study, including dermatologists, psychiatrists, psychologists, urologists, and dentists. Subjects were monitored in respect to adverse effects encountered not only during therapeutic phase but also after treatment cessation, for at least four months.

Results

On our sample, the most notable adverse effects encountered during therapeutic phase were as follow: depression (8,33%), gastrointestinal disturbances (5,95%), decreased libido (7,14%) and erectile dysfunction (2,38%). At four months after finasteride cessation, the “post-finasteride” syndrome was represented by depression (4,76%), erectile dysfunction (1,19%) and ejaculation disorders (2,38%). The subjects included in the study received no additional treatments after finasteride cessation.

The gingivo-parodontal lesions were encountered during finasteride administration at 21,42% subjects: 6 with mucosal pallor, 5 with erythema, 3 with purpura, 2 with periodontal inflammation, and 2 with gingival hypertrophy. Excepting the two patients with gingival hypertrophy who required discontinuation of finasteride to be ameliorated (regressing totally in less than three months after finasteride cessation), the other oral lesions were treated through specific/local procedures, without to be necessary to stop the finasteride administration.

Discussion

Androgenic alopecia affects nearly 30% of men under 30 years, 50% of men over 50 years and surprisingly, about 40% of women over 50 years

(8). It is in part genetically determined, being augmented by specific hormonal factor like androgens (particularly DHT) that are essential for the progression of this condition. Frontal skin contains large amounts of 5 α -reductase, the androgen-dependent processes from this level (DHT binding to the specific receptors) leading to androgenic alopecia. The onset of the affection is often gradual. Men have thinning hair in the temporal areas, the shape of the anterior scalp changing. The disease evolves progressively towards the frontal area and vertex (9).

For women it is common a diffuse hair loss, and usually in a lesser degree than in men (women generally maintaining a frontal hair line). Women should not handle finasteride tablets during pregnancy due to potential risk to a male fetus. When received the drug for idiopathic hirsutism, women recorded a hirsutism score that improved significantly after 6-9 months after the therapy onset (10).

Pharmacologically, finasteride is a 5 alpha-reductase inhibitor which acts selectively on type II and III isoenzymes. It is a partial inhibition of DHT synthesis, due to the fact that finasteride doesn't inhibit the type I of 5 alpha-reductase isoenzyme. Consequently, the conversion of testosterone to dihydrotestosterone is partially inhibited, serum level of DHT decreasing after finasteride administration with about 65–70% (11).

Finasteride adverse effects described in literature differ from study to study. Thus, the genitourinary symptoms seems to be not only physical but also functional, represented by penile and scrotal shrinkage and numbness, decreased semen volume and force, erectile dysfunction, decreased libido, and decreased or loss of orgasm (12, 13).

Mental and neurological troubles consist in memory impairment, decreased comprehension, depression, anxiety, suicidal thoughts, insomnia, anhedonia and emotional flatness (14, 15).

Physically, finasteride adverse effects are represented by gynecomastia (female-like enlargement of the breast), chronic fatigue, muscle twitching and atrophy, decreased body temperature, increased fat deposition/ elevated body mass index, cardiovascular impairments (palpitations, hypotension), dermatologic and oral manifestations (chronically dry, pruritus, rash, urticaria, erythema, purpura, gingival hypertrophy) (16, 17).

It seems that the nature and frequency of the above described adverse effects depend not only by the study design but also by the sample studied. Just an example, it was found that the frequency of finasteride side effects would be significantly higher when the patients are informed (before treatment) about the possible adverse effects, and

lower/ ignored if the patients would not be advised (18).

A lot of adverse effects related to finasteride are encountered not only during Finasteride administration but also after treatment cessation, in the form of post-Finasteride syndrome. In other words, the post-Finasteride syndrome should be delineated (as a distinct pathophysiological entity) by the adverse effects which are encountered during Finasteride administration. Adverse effects encountered during finasteride administration would be the consequences of a direct finasteride action, and indirect consequences of subsequent hormonal interferences. After finasteride cessation, adverse effects should be assigned only to the residual hormonal interferences, represented by altered level of certain neuroactive steroids in cerebrospinal fluid and plasma. In support of this delineation between finasteride and post-finasteride adverse effects, recent studies show that the frequency of finasteride side effects (occurring during Finasteride administration) is greater in right handed men, while the post-finasteride syndrome is encountered with a similar frequency in right and left handed men (7, 12, 19).

A lot of general conditions have (in different developmental stages) significant effects at the level of oral cavity. The most notable diseases are represented by: chronic hepatitis, chronic renal diseases, chronic heart failure, venous

insufficiency, malignant tumors, nutritional diseases and diabetes, immunologic diseases, etc (20, 21).

In addition, there are described more than a hundred drugs which may cause side effects to the oral mucosa/ marginal periodontium when are administered in the curative or symptomatic treatment of previously mentioned affections. Pharmacological classes including drugs with oral side effects are represented by: antidepressants, antipsychotics, antihistamines, diuretics, antihypertensives, muscarinic antagonists, anti-inflammatories, bronchodilators, muscle relaxants, antimigraine drugs, opioids, benzodiazepines and hypnotics, H₂ antagonists and proton-pump inhibitors, cytotoxic medications, retinoids, anti-HIV medication and cytokines (alpha interferon) . Clinical manifestations dependent by: drug type, dose, the degree of cumulative toxicity, patient particularities, etc. These reactions can occur immediately, or after days, weeks or months from administration onset (22).

In respect to adverse effects from oral cavity we found on our sample (consisting in eighty four subjects) that the finasteride adverse effects were encountered only during finasteride administration, being represented by mucosal pallor (6 patients), erythema (5 patients), purpura (3 patients), periodontal inflammation (2 patients) and gingival hypertrophy (2 patients). Excepting gingival

hypertrophy (who required discontinuation of finasteride administration), all oral lesions were treated through specific/ local procedures, without to be necessary to stop the drug administration. No oral lesions were identified on our sample at three months after finasteride cessation (as possible signs and/or symptoms of post-finasteride syndrome).

Finasteride and levamisole decrease the conversion of testosterone to DHT; in addition, these drugs inhibit alkaline phosphatase, an enzyme that stimulates the synthesis of DHT (23). Conversion of testosterone to DHT is increased in gingival inflammation. Yet, DHT is considered to be an important stimulator of fibroblast activity (24). Starting from these findings, some authors suggested that finasteride can be used in the form of topical application (in a suitable vehicle) to partially block the proliferation of fibroblast hyperplasia following phenytoin administration (23).

Testosterone-specific receptors have been isolated from periodontal tissue levels (25). The number of receptors in the gingival fibroblasts tends to increase inflammation or gingival hyperplasia (26). At the gingival level, testosterone stimulates the matrix synthesis via osteoblasts and fibroblasts from periodontal ligament (26- 29), stimulates the proliferation and differentiation of osteoblasts (30), reduce the production of IL-6

during inflammation through inhibition of prostaglandin (31- 33), increase the concentration of osteoprotegerin (34).

As a conclusion, finasteride adverse effects encountered on our sample at the level of marginal periodontium could be the consequences of a direct finasteride action, and possible indirect consequences of subsequent androgenic interferences.

Conclusions

Male androgenic alopecia is perceived by some men as a stressful condition, many affected persons resorting usually to specialized assistance (from family physician, dermatologists) for treatment/ amelioration. The most common treatment methods are represented by minoxidil and finasteride administration, both drugs being efficiently according to clinical studies.

Even if finasteride seems to be efficiently at first glance, recent data show that this drug can lead to serious adverse effects like depressive symptoms and suicidal thoughts during finasteride administration and among former users of finasteride with persistent sexual side effects. For this reason, it was recommended for Finasteride to be carefully administered to patients presenting a history or a high risk to developing depression (35).

In respect to our results, finasteride adverse effects encountered to oral cavity were mild to moderate, and generally responded to topical procedures without to require the stop of the drug administration. New studies on large samples will further document the existing relation between the described oral adverse effects and the implied pathophysiological mechanisms (direct consequence of finasteride administration, indirect consequences due to hormonal interferences, or no relation to finasteride). Yet, new studies should investigate if the subgroup of persons susceptible to develop finasteride adverse effects could be identified prior to finasteride administration, using individual predictive factors (36).

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