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THERAPEUTIC CONSIDERATIONS RELATED TO FINASTERIDE ADMINISTRATION IN MALE ANDROGENIC ALOPECIA AND BENIGN PROSTATIC HYPERPLASIA

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Abstract

Finasteride has been used extensively until now as a relative efficient therapeutic option for male androgenic alopecia and benign prostatic hyperplasia. Unfortunately, over time several concerns appeared regarding the frequency and magnitude of adverse effects, which in some cases have been even irreversible. Herein we review the recent literature on this topic, trying to clarify the current safety profile of Finasteride for these two therapeutic indications. We concluded that Finasteride could be retained as a therapeutic approach for male androgenic alopecia, based on two important reasons. First, a synergistic action between a partial inhibitor of 5 α -reductase (Finasteride) and another compound (like Minoxidil) are preferable to a complete suppression of 5 α -reductase (see Dutasteride), in order to preserve the important physiological roles of dihydrotestosterone. Second, Finasteride side effects can currently be addressed in part prior to the onset of the therapy, by using information about the patient such as hand preference and sexual orientation to predict the risk of adverse effects.

Rezumat

Finasterida a fost utilizată pe scară largă până acum pentru alopecia androgenică masculină și hiperplazia benignă de prostată, fiind o opțiune terapeutică relativ eficientă. Cu timpul însă au apărut tot mai multe preocupări legate de frecvența și amploarea efectelor adverse, care au fost chiar ireversibile în unele cazuri. Acest articol prezintă o revizuire a literaturii de specialitate pe această temă cu scopul de a clarifica profilul de siguranță al Finasteridei pentru cele două recomandări terapeutice. Concluzia este că Finasterida ar putea fi menținută ca și soluție terapeutică pentru alopecia androgenică masculină, din două motive importante. Primul aspect vizează menținerea rolurilor fiziologice specifice dihidrotestosteronului, pentru care ar fi de preferat o acțiune sinergică între un inhibitor parțial de 5 α -reductază (Finasterida) și un alt compus precum Minoxidil, față de o suprimare completă a 5 α -reductazei (specifică Dutasteridei). Cel de-al doilea element este legat de reacțiile adverse ale Finasteridei care pot fi avute în vedere chiar și înainte de începerea tratamentului, caracteristici individuale precum mâna dominantă și orientarea sexuală ale pacientului fiind corelate cu riscul și frecvența efectelor adverse.

Keywords: finasteride, safety profile, androgenic alopecia, benign prostatic hyperplasia

Introduction

Male androgenic alopecia and benign prostatic hyperplasia are relatively common conditions encountered in elderly male subjects. Their occurrence and progression are partly supported by the androgenic action of male sex hormone, dihydrotestosterone (DHTT). Consequently, several drugs like Finasteride and Dutasteride that interfere with DHTT synthesis have been evaluated and implemented as therapeutic solutions to ameliorate these two conditions [3, 17]. The pharmacologic action of Finasteride (especially its efficacy in decreasing levels of DHTT) has been

demonstrated through laboratory tests assessing cerebrospinal fluid and plasma in populations of men receiving Finasteride [4, 15]. However, recent studies suggest that Finasteride side effects seem to be encountered only in a subset of men [7, 16], with the aggregation of Finasteride adverse effects apparently related to lateralization processes of the brain [24, 25]. As a consequence, Finasteride use and monitoring should take into consideration not only the general pharmacological properties (pharmacokinetics and pharmacodynamics) of the drug, but also specific patient characteristics that are linked to lateralization

process of the brain such as hand preference and sexual orientation.

Indeed, recent data suggest that hand preference (left or right) and sexual orientation may be associated with the occurrence and severity of Finasteride adverse effects [24, 25]. In such predisposed men, Finasteride administration is relatively difficult to manage due to the variety and magnitude of adverse effects, (including but not limited to severe depression and sexual dysfunctions associated with suicidal thoughts) as well as their indefinite and irreversible persistence even after cessation of pharmacological action (commonly referred to as post-finasteride syndrome) [5, 14, 15, 36]. This paper presents the pharmacological profile of Finasteride and the corresponding neurobiological substrate able to explain the occurrence of various Finasteride side effects among different populations of patients. Such information could help provide the basis for reconsidering the therapeutic safety profile of Finasteride in the treatment of male androgenic alopecia and benign prostatic hyperplasia.

Pharmacological profile of Finasteride

Finasteride is a partial inhibitor (only type II) of 5 α -reductase enzyme, which converts intracellular testosterone to dihydrotestosterone. This enzyme is encountered in the sebaceous glands and liver (type I isoenzyme), and also in prostate, seminal vesicles, and hair follicles (type II isoenzyme). After Finasteride administration, the serum DHTT concentration decreases up to 70%, indicating that the type II isoenzyme generates about two-thirds of the circulating DHTT, whereas the type I isoenzyme is responsible for only one-third of the circulating DHTT [31].

In men with male androgenetic alopecia there are high amounts of DHTT and also miniaturized hair follicles in the balding scalp, compared with the hairy scalp. By reducing DHTT, Finasteride interrupts an important factor implied in the occurrence of androgenetic alopecia, which is considered a genetically predisposed condition. In patients with benign prostatic hyperplasia, the prostate volume decreases during Finasteride administration by approximately 20%, returning often to the baseline value about three months after discontinuation of therapy [22, 35].

Finasteride absorption is not affected by food, presenting a bioavailability around 65%. The maximum plasmatic concentration is reached about 1 to 2 hours after administration, ranging between 4.9 - 13.7 ng/mL for 1 mg/day, and between 27 - 49 ng/mL for 5 mg/day. After successive doses, there is a slow accumulation phase for Finasteride, with 90% of the circulating drug bound to plasma proteins.

Finasteride crosses the blood-brain barrier, a property that explains many Finasteride side effects such as mental and sexual impairments. It is extensively metabolized by the liver, especially through cytochrome

P450 3A₄ enzyme subfamily. The corresponding metabolites possess no more than 20% inhibitory activity for 5 α -reductase comparable to Finasteride action. Oral administration of Finasteride leads to its excretion in urine as metabolites (about 39%) and through faeces (57%, in part unmetabolized). The mean terminal half-life of finasteride in men between 45 - 60 years is approximately 6 hours, though longer in men over 70 years (about 8 hours) [44].

Finasteride administration produces a relatively rapid decrease of serum DHTT concentration within 6 - 8 hours, which persists over the 24-hour dosing interval, or longer for repeated administration. Daily dosing of finasteride has been shown to suppress serum DHTT concentration by approximately 65% for a 1 mg tablet, and 70% for 5 mg. Compared to baseline, the mean circulating levels of testosterone and estradiol increase up to 15%, remaining however for most subjects within the physiologic range. In a similar manner, the luteinizing hormone (LH) and follicle stimulating hormone (FSH) increase during Finasteride administration by about 10%, without exceeding the physiological level. Thus the hypothalamic-pituitary-testicular axis is not affected. No effect has been reported on thyroid-stimulating hormone, cortisol, prolactin, plasma lipid profile or bone mineral density [1, 36].

Finasteride side effects are the consequence of its direct actions on the brain and peripheral organs (nausea, vomiting, allergies, etc.), and due to indirect actions of the drug through dihydrotestosterone and possible GABA receptors [36]. The most frequent adverse effects are represented by mental (depression, suicidal ideations, anhedonia, lack of mental concentration, etc.) and sexual (impotence, erectile dysfunction, decreased libido, ejaculation disorders) impairments. Other adverse effects are also possible: insomnia, gynecomastia, chronic fatigue, elevated body mass index, pruritus, rash, urticaria, angioedema, gingival hypertrophy, etc. (Table I) [21, 30].

Finasteride also seems to change tolerance to ethanol in many individuals, with former users of finasteride reporting a decreased tolerance to alcohol [14, 46]. Finally, studies have noted several concerns related to association or even possible causal relationship between finasteride administration and high-grade prostate cancers, or male breast cancer [19, 39].

Therapeutic window and therapeutic opportunity of Finasteride

General data regarding Finasteride administration

Finasteride was introduced primarily as a therapeutic solution for benign prostatic hyperplasia (5 mg daily), ameliorating specific symptoms such as night time urination, decreased flow, prolonged initiation, etc. [40].

Table I

Finasteride adverse effects (administration: four months or more) [21, 36]

Adverse effects	Finasteride, 1 mg (%)	Placebo (%)	Finasteride, 5 mg (%)	Placebo (%)
Depression	11.76	3.92	7.44	3.19
Anhedonia	21.56	4.90	19.14	5.31
Lack of mental concentration	17.64	8.82	20.21	11.07
Suicidal ideations	5.88	0	3.19	1.06
Impotence	7.84	1.96	9.57	2.12
Decreased Libido	16.66	2.94	22.34	5.31
Ejaculation Disorder	6.86	0.0	8.51	1.06
Gynecomastia	4.90	0	6.38	1.06
Rash	2.94	0.98	4.25	1.06
Pruritus	3.92	0.98	3.19	2.12
Gingival hypertrophy	1.96	0	1.06	0

After five years, Finasteride was also approved and introduced for the therapeutic management of male androgenic alopecia (at a dose of 1 mg/day) due to its effect of improving hair stretch by up to 20 - 30% [8].

These therapeutic effects are usually obtained six months or more after finasteride administration, being maintained only so long as the drug is administered [35]. Such prolonged administration increases the therapeutic benefits of the drug, but unfortunately also the frequency and magnitude of adverse effects [36]. Some adverse effects were noted from the drug's outset during preclinical studies, while others were noted later (during the post-market experience) [46].

A comprehensive and historically accurate approach has revealed two distinct findings. First, Finasteride side effects are encountered not only during Finasteride administration but also after discontinuation, known as the post-Finasteride syndrome [36]. Second, it has been observed that some men tolerate Finasteride quite well, with only a subgroup of patients developing notable and eventually irreversible adverse effects (severe depression, sexual dysfunctions, suicidal thoughts, etc.), requiring drug discontinuation [7, 16]. For these two reasons several authors have suggested that Finasteride administration should be re-evaluated [46].

Therapeutic window and therapeutic opportunity of Finasteride

The 'therapeutic window' typically refers to the pharmacological evaluation of a drug (in terms of optimal biological dose/ time) so as to produce optimal efficacy while remaining in the range of acceptable toxicity/ adverse effects. When the therapeutic effect is insignificant and/ or toxicity (adverse effects) becomes unacceptable, the value of the drug becomes questionable [32]. In the case of Finasteride, preliminary data on patient complaints during the post-market period suggested that adverse effects were occurring more frequently than initially assumed, with greater severity and persistence, sometimes indefinitely even after the treatment was

terminated [5, 14]. For these reasons, the therapeutic window of Finasteride appeared to warrant re-evaluation (a relatively difficult process through the classical tools) [46].

The "therapeutic opportunity" is generally applied to preliminary investigations designed to evaluate the opportunity of a drug for certain diseases/ patients [33]. In the case of Finasteride, after its initial use, a second perspective evolved based on observations that severe and persistent adverse effects were encountered only in select patients; other patients reported no complaints with respect to drug administration [7, 16]. As a consequence, the second perspective maintained that the therapeutic window was relatively safe for some patients (reporting no adverse effects), and further, that the therapeutic opportunity was actually the issue of concern, and it therefore should be reconsidered for the subgroup of patients susceptible to developing severe adverse effects [24, 25]. But this process implies the formulation of relevant criteria that differentiate this highly susceptible subgroup of patients from those less or non-susceptible. So far, two potential criteria have been identified - hand preference and sexual orientation - that can help predict the severity and type of adverse effects in men under treatment [24, 25]. To understand why some men respond with severe adverse effects while others do not present adverse effects requires an understanding of the neurobiological system supporting this dual response.

The neurobiological substrate responsible by distribution of Finasteride side effects

Anatomically, the human brain is divided by the median plane into two different (left and right) hemibrains. Each cerebral event is processed usually in only one hemibrain (identified as the dominant hemibrain), the opposite hemibrain supporting only the neurological connection between dominant hemibrain and peripheral receptors/ effectors [29]. This asymmetric functioning of the brain is known as lateralization, being possible from a physiologic perspective through intervention of different neuro-

modulators that channel environmental information towards either the left or the right hemibrain [18, 37]. Without such preferential channelling, the left and right hemibrains could receive, process, and elaborate two distinct responses (competitive or, even more problematic, contradictory) to the same external stimulus/information, an eventuality that would be not only inefficient, but also counter-productive [29].

With respect to sexuality, oestrogens modulate environmental inputs especially toward the left hemibrain. As a consequence, women exposed prenatally to the synthetic oestrogen diethylstilbestrol are more likely to be left handed for writing during development [41]. By the same rationale, administration of antioestrogens such as Tamoxifen induces sexual impairments especially in left handed men [2, 26]. At the other end of the spectrum, androgens channel the same environmental information/inputs toward the contralateral/right hemibrain [9]. In this respect, administration of Finasteride or Bicalutamide induces sexual dysfunction predominantly in right handed men [23, 27]. During puberty, cortical maturation entails especially the left hemibrain in human males, while in human females this maturation involves predominantly the right hemibrain [28, 36].

Regarding the lateralized action of pheromones, in heterosexual men (sensitive to female pheromones) the process of sexual activation involves especially the right hemibrain (right hippocampus, right parahippocampal gyrus, etc.). In contrast, in homosexual men (sensitive to male pheromones) the process of sexual activation implies predominantly the left hemibrain (the left angular gyrus, left caudate nucleus, etc.) [11]. In support of this lateralized process, heterosexual men and homosexual women (lesbians) present a rightward volumetric cerebral asymmetry (their connections being more widespread from the right amygdala), while homosexual men and heterosexual women display more widespread connections from the left amygdala [38]. In addition, empirical evidence indicates that homosexual and heterosexual men are different regarding the sizes/volume of hypothalamic nuclei [20].

Finasteride side effects according to lateralized process of the brain

Returning to Finasteride administration in men, sexual side effects are directly linked to decreasing levels of DHTT. But the action of DHTT is strongly related (through the right hemibrain) to a right handed preference and female sexual pheromones/heterosexual orientation. As a consequence, it is not surprising that sexual side effects of Finasteride are correlated with hand preference and sexual orientation. In other words, hand preference and sexual orientation could be used (prior to the treatment) as possible eligibility criteria for selecting patients

having a low risk for developing sexual side effects to 5 α -reductase inhibitors like Finasteride.

Similar to sexual dysfunctions, psychological/cognitive impairments resulting from Finasteride administration are also directly related to lateralization processes in the brain. Specifically, existing interrelations between cognition and sexuality [29] can be highlighted through several poignant examples. For example, depression is closely related to estrogenic action, being more frequently encountered in women than men [34]. In addition, the incidence of depression (associated with an inter-hemispheric imbalance) is higher in left handed persons who present a hyperactive right-hemisphere, due perhaps to an inadequate or, alternatively, excessive activation of the left hemibrain under estrogenic neuromodulation [6]. We limited the discussion above to the depressive and sexual side effects of Finasteride, ones that are sometimes severe and among those encountered more frequently (being interrelated through lateralization process of the brain). These processes may set up a vicious neuro-endocrine cycle, with each (depressive and sexual side effects) maintaining or intensifying the other, and sometimes can persist indefinitely after Finasteride cessation [36]. Beyond these effects, Finasteride can also induce other adverse effects that are related either to the direct presence and action of the drug (pruritus, rash, urticaria, gingival hypertrophy, etc.), or to other mechanisms that are not hormonally mediated. As an example, Finasteride administration may affect tolerance to ethanol (through GABA_A receptors), with many former users of finasteride reporting decreased tolerance and disturbing effects from alcohol consumption (leading some men to stop drinking entirely) [13, 46]. Other studies show that Finasteride blocks the effects of dopamine receptors in the *nucleus accumbens*, having thus a therapeutic potential for certain neuropsychiatric disorders like schizophrenia [42].

Summarizing, the therapeutic approach of male androgenic alopecia and benign prostatic hyperplasia with Finasteride presented four successive phases. The initial period was represented by approval and introduction of the drug into clinical practice. The enthusiasm generated and sustained by initial therapeutic results was followed by a second, early post-market period of patient complaints of increased, more severe, and even irreversible adverse effects that continued even after Finasteride cessation [46]. The third phase involved identifying of alternative or personalized therapeutic solutions for male androgenic alopecia and benign prostatic hyperplasia, with fewer side effects and eventually superior therapeutic results [3, 35]. Thus, Dutasteride was often used as a replacement for Finasteride in the therapeutic approach of benign prostatic hyperplasia [3], a trend that was extended to androgenic

alopecia as well [8, 45]. Finally, the last phase - the one that is currently emerging - suggests that Finasteride should be reconsidered as a therapeutic approach of androgenic alopecia [36].

Conclusions

In conclusion, Finasteride could be further retained as a therapeutic approach of male androgenic alopecia, based on three important reasons.

First, male androgenic alopecia and benign prostatic hyperplasia are only partly supported by DHTT (other factors being also involved) [43], and DHTT has its own important physiological roles within the body [12]. Consequently, it makes more sense physiologically to suppress DHTT synthesis only partially (as Finasteride does) rather than almost completely (as Dutasteride does). However, to increase the therapeutic effects of Finasteride, we suggest that the synergistic actions of drug combinations (Finasteride plus Minoxidil, for example, for androgenic alopecia) [10] could provide a more suitable resolution than maximizing a single drug effect (e.g., severe suppression of DHTT by replacing Finasteride with Dutasteride).

Second, even if Finasteride adverse effects are more frequent or severe than initially assumed, recent evidence suggests that such adverse effects are (at least in part) predictable, meaning that screening of patients on *a priori* criteria (according to current and forthcoming criteria) could lead to a better compliance by patients.

Finally, adverse effects induced by Finasteride are still being documented and studied, a difficult task given that neither mental or sexual functions (often affected in tandem by Finasteride) on one hand, nor postfinasteride syndrome on the other hand, have been completely described. Understanding their link will require additional investigations regarding symptomatology and the optimal therapeutic approach to address the adverse effects [5].

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