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RESEARCH ARTICLE

IMPACT OF FINASTERIDE AND TAMSULOSIN HYDROCHLORIDE ADMINISTRATION ON SEX HORMONES, PROSTATIC MARKERS AND NEUROTRANSMITTERS IN MALE RATS

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ABSTRACT

Benign prostatic hyperplasia (BPH) is a common disease among older men. Finasteride and tamsulosin hydrochloride drugs are used in BPH treatment. This study aimed to evaluate the side effects of both finasteride and/or tamsulosin hydrochloride administration on sex hormones, prostate markers and neurotransmitters in male rats. The study was carried out on a total of sixty male rats were divided equally into four groups. Group I was the control group. Groups II and III were rats administered with finasteride and tamsulosin hydrochloride, respectively. Group IV included rats administered with both finasteride and tamsulosin hydrochloride. Results showed that serum testosterone, DHT levels and sperm count were lower than normal in all rats administered with finasteride or/and tamsulosin hydrochloride. Serum PSA level and acid phosphatatse activity showed insignificant decrease in group II and increase in group III. Prolactin levels showed insignificant increase in all groups. Neurotransmitters as dopamine and acetylcholine esterase activity showed significant decrease in all treated rats. In conclusion, tamsulosin hydrochloride has higher harmful side effects than finasteride in rats, represented in disturbances in prostatic biomarkers and testis functions and neurotransmitters. Combination therapy of both finasteride and tamsulosin hydrochloride can be considered safer than only tamsulosin hydrochloride administration.

INTRODUCTION

Benign prostatic hyperplasia (BPH) is one of the most common urinary disorders in elderly men. The symptoms of the disease include prostate gland enlargement, bladder outlet obstruction, and lower urinary tract symptoms (LUTSs). The prostate growth is dependent on the presence of hormones and growths factors. Testosterone is considered to be the most important of these and it is converted within the prostate into its more active metabolite, dihydrotestosterone (DHT), by 5α-reductase blocker, a nuclear-bound steroid enzyme which is localized primarily in the prostatic stromal cell and involved in normal and abnormal prostate growth (Smith and Carson, 2009). The number of surgical interventions performed in pharmacotherapy has significantly reduced because of the increased efficacy of conservative therapy, including combination treatment mostly with 2 groups of drugs, namely, alpha-1-adrenolitics (tamsulosin hydrochloride) and other 5-alpha-reductase inhibitors (finasteride) with a different pharmacological activity (Zabkowski, 2010).

Finasteride is a competitive and specific inhibitor of 5α-reductase type 2 with 10-fold high affinity than type 1. Finasteride forms a stable complex with enzyme5α-reductase, blocks the conversion of testosterone to a more potent androgen, dihydrotestosterone (DHT), in the prostate, hair follicles, and other androgen-sensitive tissues, leading to the suppression of serum and intraprostatic DHT concentrations (Steers, 2001). Finasteride is widely used in the treatment of androgen-dependent diseases, specifically male pattern baldness, benign prostatic hyperplasia (BPH), and prostate cancer (De Nunzio *et al*, 2008). Many clinical trials have demonstrated that FIN is well tolerated in most patients with BPH, and adverse effects other than the decreased libido and ejaculatory and erectile dysfunctions are rare (Boyle *et al*., 1996).

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Tamsulosin hydrochloride is an alpha blocker works by blocking nerve ending called alpha receptors. This will relax the smooth muscles of the prostate and bladder. Tamsulosin hydrochloride is used also to treat benign prostate hyperplasia (BPH) in men (Sonnberg, 2003). It used to treat lower urinary tract symptoms associated with BPH and urine retention (Yamanishi *et al*, 2009). Alpha-1A blockade has a potent anti-fertility effect in male rats; on the other hand, the anti-fertility effect was accompanied by significant impairment in ejaculatory ducts (Ratensooria and Wadsworth, 2009).

The aim of this study is to evaluate the side effects of both finasteride and/or tamsulosin hydrochloride administration for two months on sex hormones, prostatic markers and neurotransmitters in male rats.

MATERIALS AND METHODS

Animals

Sixty healthy adult male rats (*Sprague dawley)* were obtained from High Institute of Public Health (Alexandria, Egypt) with average weight of 135-150g (6-8 weeks old). All animals were acclimated for two weeks, before the experimental work and maintained on a standard rodent diet (20% casein, 15% corn oil, 55% corn starch, 5% salt mixture and 5% vitaminized starch; Egyptian Company of Oils and Soap Kafr-Elzayat Egypt) and water available *ad libitum*. The temperature in the animal room was maintained at 23±2 ºC with a relative humidity of 55 ± 5%. Light was on a 12:12 hrs. Light-dark cycle. They had free access to standard laboratory and observed carefully for sings of disease, stress and mortality. Both control and experimental animals were starved 12 hrs before sacrifice.

Drugs and groups

Finasteride was obtained from SIGMA pharmaceutical industries, Egypt. Tamsulosin hydrochloride was obtained from Marcyrl pharmaceutical industries, El-Obour city, Egypt.

Sixty healthy adult male rats were divided equally randomly into four groups (15 for each). The group I included rats received no treatment and are considered as control group. The group II in which each animal was orally given finasteride at a daily dose level equal to 0.7 mg/Kg every day for eight successive weeks (Paget, 1970). The group III in which each animal was orally given tamsulosin hydrochloride at a daily dose level equal to 0.7 mg/Kg every day for eight successive weeks (Paget, 1970). The group IV included rats that were orally co-treated with both finasteride and tamsulosin hydrochloride by a dose of 0.7 mg/Kg of the both every day for eight successive weeks.

Blood samples

At the end of the experimental period, rats were euthanized with intravenous injection with sodium pentobarbital. Blood samples were individually collected from the inferior vena cava of each rat in non-heparinized glass tubes. Serum was separated by centrifugation at 3000 rpm for 15 minutes. Serum samples stored at -20 °C until used in the biochemical analysis.

Epididymal sperm count and abnormalities

Epididymal sperms were collected by slicing the cauda region of epididymis in 5 ml of saline and incubated for 5 minutes at 37 º C to allow sperm to swim out of the Epididymal tubules. Sperm count and abnormalities were performed using homocytometer. Concentration of spermatozoa (sperm/ ml) was calculated from the mean number of sperm in five high powers microscopically fields under magnification of 400 X. This number multiplied by 10^6/ ml (Smith and Mayer, 1955). Images of sperms were captured by a digital camera (Cannon 620). Brightness, contrast and analysis of the images were adjusted using Adobe Photoshop software (version 4.0.1; Adobe Systems, Mountain View, CA).

Biochemical analysis

Testosterone and DHT was determined by using ELISA kit of Biovender Company. Serum samples of 10 µl and 50 µl were used for determination of testosterone and DHT levels, respectively.

PSA was measured by using an automated quantitative test for use on the VIDAS family instruments using Enzyme Linked Fluorescent Assay (ELFA) technique according to recommend method of Zhang *et al* (1995). The fluorescence is measured at 450 nm. Total acid phosphatase was measured by using colorimetric test by the kit of Spinreact Company according to the modified method of Hillmann (1971).

The quantitative determination of serum prolactin hormone concentration in the serum performed by using a microplate immune-enzymometric assay method according to Accubind-TM ELISA Microwells product code number (725-300) by using 100µl of serum according Maddox *et al* (1991).

Dopamine was measured using the kit of Genway Biotech Inc. Company by using ELISA kit. Cholinesterase in serum was measured by the kit of Quimica-Clinica Company according to Den Blawen (1983). This method depending on the fat that cholinesterase hydrolyzes Butyryl thiocholine to give thiocholine and butyrate. The reaction between thiocholine and Dithiobis-nitrobenzoate (DTNB) produces 2-nitro-5-mercaptobenzoate, a yellow compound which can be measured at 405 nm.

Statistical analysis

Data were expressed as mean values ± SD (standard deviation) and statistical analysis was performed using one-way analysis of variance (ANOVA) to assess significant differences among treatment groups. The criterion for statistical significance was set at $p \leq 0.05$. All statistical analyses were performed using SPSS statistical version 16 software package (SPSS® Inc., USA).

RESULTS

The results obtained from this experiment showed the effect of both drugs (finasteride & tamsulosin hydrochloride) on testis by decreasing testosterone; dihydro testosterone (DHT) and sperm count in all treated groups, especially tamsulosin administered rats in comparing with the control (Tables 1). Many disturbances appeared in the sperms of rats injected with tamsulosin hydrochloride as hummer head and coiled tail, while in rats injected with finasteride had normal sperms. rats injected with both finasteride and tamsulosin hydrochloride showed few abnormalities as slight coiled tail (Figure 1).

Finasteride has protective effects on prostate appeared as decreasing in prostate specific antigen (PSA) level and total acid phosphatase activity in rats orally injected with finasteride. Howerver, these markers increased in case of tamsulosin hydrochloride administration. Rats administrated with both drugs showed significant increase in PSA and acid phosphatase (Tables 2).

Prolactin levels showed insignificant decrease in all treated rats. Studying of some neurotransmitters showed significant decrease in dopamine concentration and acetylcholine esterase activity in all treated groups in comparison with the control (Table 3).

Table 1 Testosterone and DHT levels and sperm count in all treated rats with finasteride and/or tamsulosin hydrochloride.

Group	Testosterone (ng⁄ml)	DHT (ng⁄ml)	Sperm Count (x 10^6⁄ml)
Gp I (Control)	21.36 ± 1.42	789.66 ± 1.52	75.00 ± 1.00
Gp II (FIN)	18.30 ± 1.41*	398.66 ± 1.53*	61.66 ± 1.52*
Gp III (TMSL)	4.83± 1.33*	189.83± 1.04*	36.33± 1.15*
Gp IV (FIN + TMSL)	14.65 ±1.60*	201.16 ±1.60*	63.00 ±2.64*

(*): significant at $p \leq 0.05$ in comparison of the corresponding group versus the control group, where FIN: finasteride and TMSL: tamsulosin hydrochloride.

Table 2 prostatic surface antigen (PSA) levels and acid phosphatase activity in all treated rats with finasteride and/or tamsulosin hydrochloride.

Group	PSA (ng⁄ml)	Acid phosphatase (U⁄L)
Gp I (Control)	3.80 ± 0.70	1.96 ± 0.75
Gp II (FIN)	3.36 ± 1.26	1.36 ± 0.30
Gp III (TMSL)	4.83± 1.81	3.53± 0.60*
Gp IV (FIN + TMSL)	5.06 ±0.25*	2.26 ±0.75

(*): significant at P ≤ 0.05 in comparison of the corresponding group versus the control group, where FIN: finasteride and TMSL: tamsulosin hydrochloride.

Table 3 Serum Prolactin levels, dopamine and acetylcholine activity in all treated rats with Finasteride and/or Tamsulosin hydrochloride**.**

Group	Prolactin (ng⁄ml)	Dopamine (ng⁄ml)	Acetylcholine esterase (U⁄L)
Gp I (Control)	0.93 ± 0.83	83.33± 2.08	78.33± 2.08
Gp II (Finasteride)	1.00 ± 0.13	49.33 ± 2.08*	40.33 ± 1.52*
Gp III (Tamsulosin HCl)	1.90± 1.36	53.33± 2.08*	53.00± 2.00*
Gp IV (FIN + TMSL)	1.66 ±0.37	63.66 ±2.08*	48.33 ±2.08*

(*): significant at P ≤ 0.05 in comparison of the corresponding group versus the control group, where FIN: finasteride and TMSL: tamsulosin hydrochloride.

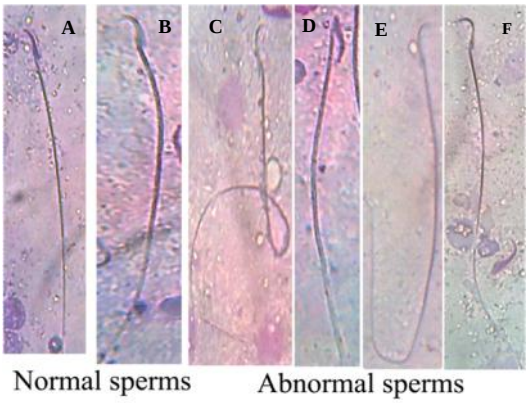

Figure 1 Photomicrographs of rat sperms. A- Sperms of control rats showed normal head and tail. B- Rats administered with finasteride had normal sperms with no changes. C & D- Rats administered with tamsulosin hydrochloride showed abnormal sperms in the neck (hummer head) and coiled tail. E & F- Rats administered with both finasteride and tamsulosin hydrochloride showed normal sperm with slightly coiled tail and abnormal neck.

DISCUSSION

The synthetic drug finasterideis a competitive inhibitor of 5α-reductase. Finasterid ereduces the conversion of testosterone to DHT in the hair follicles and thus diminishes the activation of androgen receptor by the higher affinity androgen, DHT (Jackson, 2000). Finasteride has been used in some control trials for treatment of hirsutism, hair loss, alopecia and BPH (Kaufman, 2002).Both androgenetic alopecia and BPH are androgen dependent disorders and associated with in situ high levels of intracellular DHT and increased 5α-reductase activities. As androgenic stimulation contributes to pathogenesis of both disorders, finasteride evokes a good therapeutic response by DHT suppression.

The morphological observations during this experiment indicated that, rats administrated with finasteride had increase of the body hair growth during the experimental period (eight weeks). These observations can be explained by previous studies which confirmed the conversion of testosterone to DHT by two isoforms of 5α-reductase, type I and type II (Smith and Carson, 2009).

The data obtained in this study have showed significant decrease in testosterone levels in all orally injected rats in comparison with normal values of the control group. This decrease reached to 4.5 folds in rats administered with tamsulosin hydrochloride. These results were in agreement with that of Oh *et al* (1998) who stated that finasteride administration reduces testosterone concentrations in many organs, such as prostate and hair follicles. Level of testosterone decreases through either the effect of steroidogenesis enzymes in testes, or its inactivation properties on adrenergic systems involved in steroidogenesis (Mocktary *et al*, 2007). On the other hand, some studies approved that oral administration of finasteride reduces the intraprostatic and serum DHT. This in turn results in a slightly increase in testosterone (Norman *et al*, 1993; Gormley *et al*, 1992).

DHT results obtained in the present study showed significant decrease in all treated rats in comparison with normal concentrations in the control group. Tamsulosin hydrochloride

administration showed the lowest values, the decrease reached to about 4.1 folds. These results are consistent with that of Oh *et al* (1998) who reported that, pharmacologically; finasteride inhibits 5α-reductase, the converting enzyme of testosterone to DHT in many organs, such as prostate and hair follicles. Both short and long exposure of rats to this compound has already been shown to induce a marked decrease in intraprostatic DHT levels that is followed by a reduction of the ventral lobe weight. Finasteride is thought to cross the blood brain barrier and inhibits 5α-reductase in the central nervous system (Lepart, 1995). Finasteride reduces serum DHT by approximately 70% (Bartsch *et al*, 2002). Moreover, morphometric analyses revealed a significant decrease in absolute volume of both glandular epithelial and stromal compartments of rat prostate with a subsequent reduction in prostate secretions (Prahalada *et al*, 1998). It has also been demonstrated that rat prostate involution observed under finasteride treatment is partly due to apoptosis and to a dramatic regression of prostate vascularization (Shibata *et al*, 2003).

Sperm count in rats administered with finasteride showed a significant decrease in comparison to normal sperm count in control group. Rats administered with tamsulosin hydrochloride showed significant decrease in sperm count reached to nearly half of its normal count. Both finasteride and tansulosin hydrochloride administered rats showed nearly slightly decrease in sperm count. Sperm count in rats orally injected with both finasteride and tansulosin hydrochloride was higher than rats administered with only finasteride or that administered with only tansulosin hydrochloride. These results are in agreement with a study of Amory *et al* (2007) who suggested that finasteride administration mildly decreases semen parameters, higher doses of finasteride used to treat BPH have been associated with a reversible decrease in total sperm counts and sperm motility in humans and previous studies have shown that finasteride administration has a reversible negative effect on spermatogenesis (sperm count, semen volume, sperm concentration, and sperm motility, significantly different from baseline). On the other hand, these findings are controversial to those of Lewis *et al* (1992) who reported no effect on spermatogenesis in men taking finasteride. In rat studies, finasteride has been shown to decrease fertility. However, this effect was felt to be secondary to inadequate copulatory plug formation, secondary to the drug's effects on seminal vesicles and the prostate (Wise *et al*, 1991). Further studies did not show any effect on spermatogenesis.

Therefore, the effects of finasteride on fertility seen in rats were felt to be a species specific (Rhoden *et al*, 2002). These findings are consistent with the previous studies reported that tansulosin hydrochloride distributed easily to sexual organs such as testes and affects negatively on the number of sperm, semen volume, semenviscosity, transportation of sperm from the testes, size of these miniferous tubules and ejaculation (Michel, 2007). Short-term treatment with tansulosin hydrochloride had a negative effect on sperm concentration, total sperm count, sperm motility, and semen viscosity in healthy men (Hellstrom and Sikka, 2009). It is well accepted that the low sperm production was in relation with the reduction in size of the seminiferous tubules (Ratensooria and Wadsworth, 1994). Thus, all these reasons may explain the dramatically reduction in the numbers and abnormal changes of sperms after treating with tansulosin hydrochloride. Naturally, the sexual hormones play a central role in decreasing spermatogenesis and the number of testes germinal cells (Shariati *et al*, 2008).

Rats administered with finasteride, rats administered with tamsulosin hydrochloride and rats administrated with both finasteride and tamsulosin hydrochloride showed insignificant increase in the prolactin hormone concentrations. There is evidence to suggest that prolactin may be involved in steroidogenesis in the gonad, acting synergistically with luteinizing hormone. High levels of prolactin appear to inhibit steroidogenesis as well as inhibiting LH and follicle stimulating hormone (FSH) synthesis at pituitary gland (Maddox *et al*, 1991; Gonzales, 2001). These results were in agreement with (Huhtaniemi *et al*, 1991) who explained the clinical observations also support a role for prolactin in the regulation of the testis and accessory gland in man. For example, suppression of gonadotrophins and prolactin secretion in eugonadal men treated for prostatic carcinoma caused a more marked reduction in testicular weight and spermatogenesis than suppression of gonadotrophins secretion alone. Prolactin binding has been demonstrated in the human prostate (Leake *et al*, 1983), and other studies suggest that prolactin may play a role in the etiology of BPH and cancer (Kadar *et al*, 1988; Nevalainen *et al*, 1997).

Our observations during this experiment showed that finasteride reduced the physical activities of the animals. Similar observation was described by Heinlein and Chang (2002) who studied that the behavioral effects mediated by finasteride and other 5α-reductaseinhibitors were observed within short time after administration, suggesting that the neuroactive steroids responsible for the behavioral effects may act through non-genomic interactions. Indeed, many neuroactive steroids are known to influence behavioral and cognitive functions through fast-acting interactions with numerous neurotransmitter systems. Antipsychotic-like effects of finasteride and other 5α-reductase inhibitors on rat models of psychotic-like behaviors were indicated. Although in humans finasteride acts as a selective inhibitor of the peripheral 5α-reductase type-2, in rats it is known to block efficiently both 5α-reductase isozymes, and is in fact generally used to inhibit neurosteroid synthesis in rats (Concas *et al*, 1998; Finn *et al*, 2006).

Prostate specific antigen (PSA) acts as a surrogate measure for prostate volume, and as a predictor for increased risk of acute urinary retention (Roehrborn *et al*, 2001). The clinical utility of PSA as a marker for prostate cancer emerged in 1980 with the initial report of elevated PSA levels in the serum of prostate cancer patients. Since this time, the use of PSA as a tumor marker has flourished and PSA has proven to be the most useful marker in urologiconcology or to identify postsurgical residual disease or tumor recurrence (Morote *et al*, 1988). In the present work, rats treated with finasteride showed significant decrease in PSA concentration. However, data

obtained from rats administered with tamsulosin hydrochloride and rats administrated with both finasteride and tamsulosin hydrochloride increase in PSA concentration. Those observations are in accordance with previous study reported that finasteride predictably reduces total PSA, an effect that appears to plateau after a period of finasteride therapy (Guess *et al,* 1996).One of the issues facing patients receiving finasteride therapy is the interpretation of PSA levels. There is some concern among clinicians that this PSA suppression may interfere with its utility in early detection as well as staging of prostate cancer (Bluestein and Oesterling, 1993).The mechanism of PSA suppression by finasteride is thought to be related to suppression of intraprostatic and serum DHT levels (Guo *et al,* 1994). In opposite to these results, a previous study reported that PSA levels in serum decreased after tamsulosin hydrochloride administration (Tubaro *et al,* 2010).

Acid phosphatase is a tissue specific differentiation antigen and produced by the glandular epithelial cells of the prostatic acini and is excreted into the glandular lumen. Acid phosphatase levels in the prostatic fluid are 50 to 100 times higher than in the serum. Prior to the identification of PSA in 1971, acid phosphatase was used as a marker for prostate cancer (Catalana, 1984). Evidence suggests that acid phosphatase may be involved in the regulation of prostatic growth through protein tyrosine phosphorylation. This phosphorylation controls cell growth through mediation of several oncogene protein products and growth factor receptors (Lin *et al,* 1992). Our results showed insignificant decrease in acid phosphatase activities in finasteride administered rats. However, in tamsulosin hydrochloride administered rats, acid phosphatase levels showed significantly increase reached to about 3 folds in comparison with normal values.

Rats administered with both finasteride and tamsulosin hydrochloride represented significant increase reached to about 2 folds in comparison with normal concentrations of control group. The mechanism for lack of acid phosphatase suppression after finasteride therapy may be related to lack of reduction in serum testosterone (Gormley *et al,* 1992). Lack of serum acid phosphatase suppression by finasteride was also noted in an earlier study of finasteride form etastatic prostate cancer (Presti *et al,* 1992). Therefore it appears that serum PSA correlates more with serum DHT levels than than serum testosterone levels. In contrast to PSA, serum acid phosphatase appears to be independent of serum DHT levels but maybe dependent on serum testosterone levels (Meng *et al,* 2000).

Dopamine agonists and dopaminergic agents have been used to treat sexual dysfunction (Kennedy and Rizvi, 2009; Balon and Segraves, 2008) and dopamine synthesis is modulated by neurosteroids (Charalampopoulos *et al,* 2005). In the present work, the results obtained from rats administrated with finasteride, rats administered tamsulosin hydrochloride and rats administrated with both finasteride and tamsulosin hydrochloride showed significant decrease in dopamine and acetylcholine esterase concentrations. These results confirmed by many previous studies indicated that 5α-reductase inhibitors reduce dopamine levels by inhibiting neurosteroid biosynthesis, that inhibition of 5α-reductase activity by finasteride influences neuronal plasticity on a structural leveland this may have serious implication on several functions including depression (Bishnoi *et al,* 2008; Bortolato *et al,* 2008). In animal model studies, finasteride treatmentled to a significant decrease in brain DHT levels and induced a reversible reduction in the number of newborn cells and young neurons in the hippocampus (Römer *et al,* 2010). Neuroactive steroids are produced in the central nervous system by transforming substrates from adrenal or gonadsteroids to active neurosteroids (Dubrovsky, 2006). It has been shown that finasteride diminishes neurosteroid biosynthesis (Finn *et al,* 2004; Vandoren *et al,* 2000). Finasteride is thought to cross the blood-brain barrier and inhibits 5α-reductases in the central nervous system (Lepart, 1995). Finasteride enhances stress-mediated release of dopamine (Dazzi *et al,* 2002), but prevents ethanol-induced increase in extracellular dopamine concentration (Dazzi *et al,* 2007).

These findings were in agreement with the observations of another study stated that tamsulosin hydrochloride selectively antagonizes α-adrenergic receptors relative to α1b-adrenergicreceptors and also has a high affinity for dopamine and serotonin receptors (Andersson and Wyllie, 2003). Most importantly, numerousstudies with endogenously released neurotransmitter as well as exogenously applied agonists have demonstrated that contraction of the human prostate is mediated predominantly if not exclusively by *α*–adrenoreceptor (Michel and Vrydag, 2006). Several additional modes of action have been proposed including effects of *α* -blockers on receptors in the spinal cord and/or the bladder. While *α*-adrenoreceptors in the central nervous system including the spinal cord can contribute to the regulation of lower urinary tract function, their role in beneficial *α*-blocker effects is difficult to reconcile with the observation that several drugs of this class, for example, tamsulosin hydrochloride, show only little penetration of the blood-brain-barrier (Wilde *et al,* 1993; Soeishi *et al,* 1990).

CONCLUSION

In conclusion, tamsulosin hydrochloride administration has higher harmful side effects than finasteride in rats. These harmful effects represented in disturbances in prostatic markers as PSA and acid phosphatase increase, testis functions decrease as testosterone, DHT and sperm count and prolactin increase and neurotransmitters decrease as dopamine and acetyl cholinesterase activity. Combination therapy of both finasteride and tamsulosin hydrochloride can be considered safer than only tamsulosin hydrochloride administration.

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