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By Anup Patil, Dr. R. C. Doijad, Dr. P. V. Salve & A. A. Koparde

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Additive Effect of Oral Tetradecanoic Acid to Tamsulosin and Finasteride in a Benign Prostatic Hyperplasia Rat Model

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Abstract- We investigated the benefit of the tetradecanoic acid combined with tamsulosin and finasteride, in a benign prostatic hyperplasia (BPH) rat model. By bilateral orchiectomy under ketamine anesthesia Castration was performed. A rat model of BPH was established by daily intramuscular administration of testosterone propionate plus 17 alpha-estradiol for 8 weeks. For 4 weeks from week 6 to 9 post-surgery model rats were administered combinations of 20 mg/kg of tetradecanoic acid, 0.01 mg/kg tamsulosin and 1 mg/kg finasteride once daily by oral gavage. Body and genitourinary organ weights were recorded, serums were assayed for hormone concentrations, and tissues were subjected to histopathology Combined tetradecanoic acid, tamsulosin, and finasteride significantly decreased prostatic index, serum hormone levels, epithelial thickness, The 3-drug combination was more effective than any other combination or tetradecanoic acid alone. These results suggest that tetradecanoic acid addition to tamsulosin and finasteride may be beneficial for the treatment of BPH patients who do not respond to tamsulosin plus finasteride.

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I. Introduction

Urinary urgency, slow stream, nocturia and increased daytime frequency various symptoms prostate enlargement.[1] Benign prostatic hyperplasia (BPH), also known as benign enlargement of the prostate, is a hormone and age-related disease characterized by histological changes in the prostate gland and variable enlargement of the prostate.[2] Negative effect on the quality of life of BPH patients considerable due to these symptoms. [3, 4] Although the pathogenesis of BPH is hormonal changes in an aging man.[5] Androgen stimulation, by dihydrotestosterone (DHT) that is a highly active metabolite of testosterone synthesized from the prostate 5 alpha- reductase enzyme responsible for development and growth of normal prostate.[6,7] Treatment options exist: alpha1-adrenergic receptor antagonists and 5 alpha-reductase inhibitors to reduce smooth muscle tone in the prostate and the bladder neck, and reduce prostate size simultaneously for patients with BPH.[8] Tamsulosin and finasteride have been the most popular medication but furthermore, these drugs induce undesirable side effects, including decreased libido, erectile dysfunction, dizziness, postural hypotension, asthenia, and occasional syncope prescribed for treating BPH.[9] McConnell et al[10] reported that only 64% of men receiving both therapies showed the reduced risk of clinical progression, defined as worsening of symptoms, acute urinary retention, incontinence and urinary tract infection.[11,12] Therefore, it is highly desirable to develop an alpha1-adrenergic antagonist or other medication that can selectively suppress the smooth muscle tone of lower urinary tract without vascular effects and decrease prostate volume without sexual dysfunction for the treatment of urinary outlet obstruction.[14] Recently oral administration of tetradecanoic acid (70 and 140 mg/kg) is used for prevention of BPH produced no clinical signs or adverse effects.[15] The purpose of this investigation was to evaluate that addition of oral tetradecanoic acid to conventional tamsulosin plus finasteride treatment can augment pharmacological efficacy in a BPH rat model.

II. Materials and Methods

a) Chemicals and reagents

Testosterone was purchased from Sigma-Aldrich. Finasteride and 17 alpha-estradiol were purchased from Sigma-Aldrich). Tamsulosin was donated by ILDONG Pharmaceutical Company (Seoul, Republic of Korea) All other chemicals were purchased from standard suppliers. Testosterone plus 17alpha-estradiol used in this study was dissolved in corn oil. tetradecanoic acid was dissolved in 10% Tween 20 buffer All animal procedures in this study were performed in accordance with the Guide for the Care and Use of CPCSEA.

b) Treatment of BPh rat model with tetradecanoic acid, tamsulosin and finasteride

A total of 42 male SD rats (250–300 g) were selected for this study. The 6 rats were incised above the pelvic region on the ventral side and then sutured without cutting off the testicles as a control group (CON ±Vehicle). The testicles of 36 male SD rats were removed under anesthesia with intraperitoneal ketamine (50 mg/kg;) and 2% xylazine hydrochloride (25 mg/kg;).

Author α σ ρ ω: Krishna Institute of Medical Sciences Deemed to be university's, Malkapur, Karad, Maharastra, India.
e-mail: anuppatil.pharma@gmail.com

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The 6 castrated rats were intramuscularly administered corn oil (CAS+Vehicle). A week after castration, 30 rats were intramuscularly administered testosterone (3 mg/kg) plus 17β-estradiol (0.03 mg/kg) daily for 8 weeks to induce BPH. The 30 castrated BPH rats were then randomly assigned to 5 experimental groups: Positive control group (BPH+Vehicle), tetradecanoic acid-treated (BP+T), tetradecanoic acid and tamsulosin-treated (BPH+TT), tetradecanoic acid and finasteride-treated (BPH+TF) and tetradecanoic acid tamsulosin and finasteride-treated (BPH+TTF). Treatment groups received the indicated combination of tetradecanoic acid (20 mg/kg), tamsulosin (0.01 mg/kg) and/or finasteride (1 mg/kg) once daily for 4 weeks from week 6 to 9 post-surgery. The volumes of administration were 6 mL/kg for oral administration and 0.7 mL/kg for intramuscular injection, respectively. The volumes were calculated based on recent weights.

c) *Sample collection*

Blood was obtained from the abdominal vein. Organs such as the prostate, bladder, penis and seminal vesicles were surgically removed. Prostate volume was measured and the prostatic index was calculated as prostate volume/body weight X100.

i. *Measurement of hormone levels in the serum*

Serum levels of DHT, testosterone, were measured using commercial kits. All protocols were performed according to the manufacturer's instructions.

ii. *Histopathological examination*

Fixed prostate tissues embedded in paraffin wax were cut into 4 cm thick sections and stained with hematoxylin (Sigma- Aldrich) and eosin (Sigma-Aldrich). The sections were mounted and cover-slipped using mounting medium and then examined under a microscope.

iii. *Statistical evaluation*

All analyses were performed using SPSS version 12.0. Values are expressed as mean ± SD. Differences among treatment group means were tested by analysis of variance and post-hoc Duncan's multiple range tests. A *P*-value > 0.05 was considered statistically significant for all tests.

III. Results

a) *Effects of tetradecanoic acid, tamsulosin and finasteride combinations on body and genitourinary organ weights*

Body weight at 1 week post-castration did not differ among the groups (Table 1). However, body weight at 9 weeks post-castration was significantly lower in the disease control group compared to the castration group (CAS±Vehicle) and the sham-operated control group (CON±Vehicle). The absolute prostate volume and prostatic index were significantly lower in the BPH±L group than the disease control group and lower still in the group receiving all three drugs (BPH±LTF group).

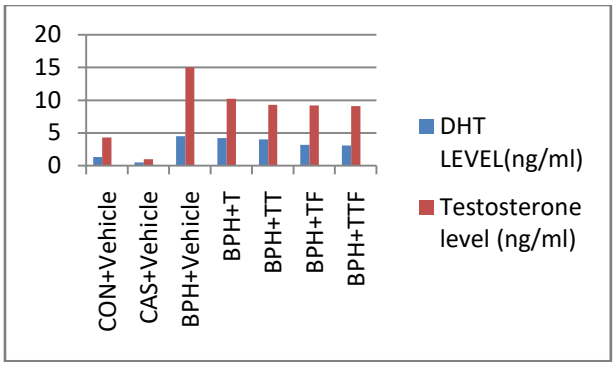
Table 1: Changes in weights of body and genitourinary organs

Group	Prostate volumes		Penis (g)	Seminal vesicle (g)	Bladder (g)	Body weights (g)	
	Absolute volume (g)	Prostatic index				1 week	9 week
CON+Vehicle	0.78±0.25^{d}	0.22±0.06^{c}	0.44±0.08^{c,d}	0.42±0.07^{d}	0.17±0.04^{c}	329.33±24.73	423.10±13.40^{a}
Cas+Vehicle	0.14±0.04^{e}	0.03±0.01^{d}	0.25±0.07^{e}	0.14±0.06^{e}	0.08±0.02^{b,c}	331.57±13.99	415.05±06.74^{a}
BPH+Vehicle	1.90±0.30^{a}	0.58±0.14^{a}	0.45±0.05^{a}	0.76±0.14^{a}	0.24±0.06^{a}	336.00±08.53	349.45±12.57^{b}
BPH+T	1.41±0.08^{b}	0.42±0.03^{b}	0.54±0.07^{a,b}	0.67±0.08^{b}	0.21±0.07^{a,b}	347.20±04.55	354.01±09.74^{b}
BPH+TT	1.45±0.13^{b}	0.40±0.05^{b}	0.32±0.08^{b,c}	0.66±0.10^{b,c}	0.17±0.09^{a,b}	339.00±12.49	348.55±08.53^{b}
BPH+TF	1.37±0.11^{b}	0.38±0.02^{b}	0.42±0.05^{c,d}	0.58±0.13^{b,c}	0.15±0.04^{b,c}	339.80±22.53	352.31±10.12^{b}
BPH+TTF	1.13±0.12^{c}	0.33±0.05^{b}	0.43±0.12^{d}	0.57±0.10^{c}	0.15±0.03^{b,c}	330.83±23.58	355.78±23.74^{b}

Notes: Values with different superscript alphabets in the same row are significantly different (P < 0.05) by one-way analysis of variance and the Duncan's multiple range tests. Abbreviations: BPH, benign prostatic hyperplasia; BPH+Vehicle, Positive control; BPh+ T, tetradecanoic acid (20 mg/kg); BPh+ T T, tetradecanoic acid and tamsulosin (0.01 mg/kg); BPh+TF, tetradecanoic acid and finasteride (1 mg/kg); BPH+TTF, tetradecanoic acid, tamsulosin, and finasteride; CAS+Vehicle, castration; CON+Vehicle, control.

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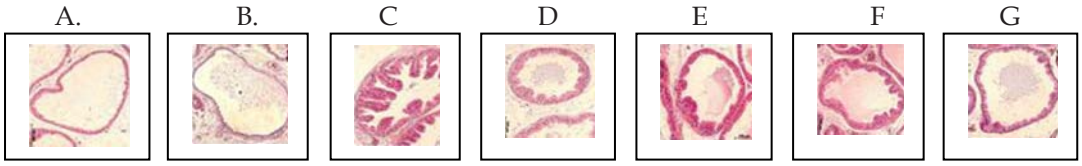
Effects of tetradecanoic acid, tamsulosin and finasteride combinations on serum hormones.



Serum DHT, testosterone, free testosterone, and estradiol levels are shown in Figure 1. Serum DHT was markedly higher in the disease control group (4.70±0.19 ng/mL) than the CON±Vehicle group (Figure 1A). However, DHT levels were significantly lower in the BPH±L group (4.06□0.59 ng/mL) and lower still in the BPH±LTF group (2.97±0.55 ng/mL) compared with the disease control group. The disease control group also exhibited significantly increased serum testosterone (15.66±2.79 ng/mL) compared with the CON±Vehicle group (3.31±1.05 ng/mL; Figure 1B). In contrast, serum testosterone levels were significantly lower in the BPH±L and BPH±LTF groups compared with the disease control group.

b) Effects of tetradecanoic acid, tamsulosin, and finasteride combinations on prostatic epithelial hyperplasia

Histopathological studies results revels the beneficial effects of tetradecanoic acid tamsulosin and finasteride on epithelial hyperplasia. Maximum hyperplasic cell are observed in C slide (BPH+ vehicle) there was maximum hyperplasia maximum proliferation of cells. Group D, E, F, G maximum protection on histoarcheture was observed.



A: CAS+Vehicle, castration, B: CON+Vehicle, control, C: BPH+Vehicle, Positive control; D: BPH+ T, tetradecanoic acid (20 mg/kg); E: BPH+ T T, tetradecanoic acid and tamsulosin (0.01 mg/kg); F: BPH+TF, tetradecanoic acid and finasteride (1 mg/kg); G: BPH+TTF, tetradecanoic acid, tamsulosin, and finasteride.

IV. Discussion

DHT is an important factor in BPH pathogenesis as it is the androgen primarily responsible for prostate growth.[16] DHT stimulates the transcription of growth factors that are mitogenic for prostate epithelial and stromal cells.[7] Finasteride, a type II 5+reductase inhibitor, that reduces epithelial cell size and the proliferative activity of DHT, is used for treating human BPH.[17] Surgical treatments, such as transurethral resection of the prostate, are performed most widely as the second option for patients who do not respond completely to combined finasteride plus tamsulosin therapy.[18] In the present study, LTF treatment reduced BPH- dependent DHT elevation to a greater extent than tetradecanoic acid alone. These results indicate that combined administration of tetradecanoic acid, tamsulosin, and finasteride have additive or synergistic anti-proliferative effects, possibly by interfering with androgen signaling. The prostatic index is used as a clinical marker of BPH development[5] and prostatic index is higher in animal models of BPH[19]. In the present study, oral administration of tetradecanoic acid, with tamsulosin and finasteride significantly reduced the prostatic index, serum hormone levels, in a rat model of BPH. Finasteride and other agents commonly used to treat BPH clinically also decrease the prostatic index.[20] The rat model established in this study exhibited an increased prostatic index compared with castrated rats, while tetradecanoic acid alone (BPH+T group) induced a reduction in prostatic index compared with the disease control group. Justulin et al [21]. These results indicate that combined administration of tetradecanoic acid, tamsulosin, and finasteride attenuated prostatic enlargement induced by testosterone plus 17+estradiol to a greater degree than tetradecanoic acid alone (or tetradecanoic acid with either tamsulosin or finasteride). BPH involves the proliferation of prostate epithelial and stromal cells, resulting in increased prostate weight and volume.[22] The prostate is connected to the urethra by

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fascia and a series of ducts in rats.[23] When the prostate is sufficiently large, it can physically compress the urethra, resulting in partial or sometimes complete obstruction.[24] The disease control group showed marked epithelial hyperplasia compared with the CON+Vehicle group, which was only mild in BPH rats treated with tetradecanoic acid alone or a combination of tetradecanoic acid, tamsulosin, and finasteride.

V. Conclusion

Combined tetradecanoic acid, tamsulosin, and finasteride significantly decreased prostatic index, serum hormone levels, epithelial thickness, The 3-drug combination was more effective than any other combination or tetradecanoic acid alone. These results suggest that tetradecanoic acid addition to tamsulosin and finasteride may be beneficial for the treatment of BPH patients who do not respond to tamsulosin plus finasteride.

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