Pharmacokinetic analysis and bioequivalence of Finasteride and Doxazosin formulated in a single tablet in comparison with the corresponding single agents

Análise farmacocinética e bioequivalência de formulação de Finasterida e Doxazozina em comprimido único em comparação com os fármacos correspondentes isoladamente

DOI:10.34119/bjhrv6n2-023

Recebimento dos originais: 24/03/2023
Aceitação para publicação: 25/04/2023

Camila Leles Guimaraes
Graduated in Chemistry
Institution: Magabi Pesquisas Clínicas e Farmacêuticas Ltda.
Address: Rodovia Presidente Castelo Branco, 3565, Ingahi, Itapevi – SP
E-mail: camila.guimaraes@magabi.com.br

Paulo Alexandre Rebelo Galvinas
Bachelor in Chemistry
Institution: Eurofarma
Address: Rua Pascoal Pais, 525, Vila Cordeiro, São Paulo – SP, CEP: 04581-060
E-mail: pargalvinas@yahoo.com.br

Juliana Almeida Baratta
Master of Pharmaceutical Sciences
Institution: Quali9 Gestão e Projetos
Address: Rua Passatempo, 210, CEP: 30310-760, Anchieta, Belo Horizonte - MG
E-mail: julianaabaratta@gmail.com

Guilherme Araújo Pinto
MBA Business Management
Institution: Eurofarma Laboratórios S.A.
Address: Rodovia Presidente Castelo Branco, 3565, Ingahi, Itapevi – SP
E-mail: guiap7@gmail.com

Amanda Hayashi Brandão
Specialist in Quality Management Systems
Institution: ATCGen
Address: Rua Francisco Glicério, 1326 conj. 64 Centro, Campinas – SP, CEP: 13012-905
Email: amanda@atcgen.com.br

Carlos Sverdloff
Master of Science in Clinical Pharmacology
Institution: ATCGen
Address: Rua Francisco Glicério, 1326, Conj. 64, Centro, Campinas – SP, CEP: 13012-905
E-mail: carsver@atcgen.com.br

Vinicius Marcondes Rezende
PhD in Medical Sciences
Institution: ATCGen
Address: Rua Francisco Glicério, 1326, Conj. 64, Centro, Campinas – SP, CEP: 13012-905
E-mail: vinicius@atcgen.com.br

ABSTRACT
The most commonly agents used to treat benign prostatic hyperplasia (BPH) in clinical practice are finasteride and doxazosin employed alone or in combination. Randomized clinical trials have shown that combination therapy with finasteride and doxazosin is superior to finasteride alone or placebo. However, decreased patient compliance may lead to unsatisfactorily therapeutic results. The aim of this study was to assess whether the combined pharmacokinetic profile for both finasteride and doxazosin was not significantly altered when these agents were co-administered, in comparison with their use as single agents. This was a randomized 6 sequences and 3 periods, crossover, comparative study of three medications: finasteride (5 mg), doxazosin (2 mg) (references), and the fixed combination containing 5 mg of finasteride and 2 mg of doxazosin in a single tablet (test). Plasma samples obtained from 30 eligible subjects were analyzed simultaneously for finasteride and doxazosin by HPLC coupled to a LC-MS/MS having cyproterone acetate and terazosin as internal standards. The statistical analysis showed no significant differences for $AUC_{0\text{-}72h}$ (finasteride: 245.3±87.8 vs. test: 240.5±93.1 and doxazosin: 183.0±42.9 vs. test: 188.8±45.6 ng.h.mL^{-1}), $AUC_{0\text{-}\infty}$ (finasteride: 247.4±92.1 vs. test: 40.47±93.1 and doxazosin: 190.3±44.3 vs. test: 188.8±45.6 ng.h.mL^{-1}), and C_{max} (finasteride: 34.2±7.1 vs. test: 29.9±6.2 and doxazosin: 16.3±3.6 vs. test: 14.9±3.3 ng/mL). The mean ratios of $AUC_{0\text{-}72h}/AUC_{0\text{-}\infty}$ for finasteride and doxazosin were 99.99% and 99.98%, respectively, indicating that the sampling time was adequate for both drugs. In summary, the current pharmacokinetic study demonstrated bioequivalence between the single agents and the corresponding agents in combination and provided further evidence for the lack of pharmacokinetic interaction between finasteride and doxazosin.

Keywords: Doxazosin, Finasteride, pharmacokinetics, benign prostatic hyperplasia, therapeutic equivalence, bioequivalence.

RESUMO
Os agentes mais comumente usados para tratar a hiperplasia prostática benigna (HPB) na prática clínica são a finasterida e a doxazosina, empregadas isoladamente ou em combinação. Estudos clínicos randomizados demonstraram que a terapia combinada com finasterida e doxazosina é superior à finasterida isolada ou ao placebo. Entretanto, a baixa adesão do paciente pode levar a resultados terapêuticos insatisfatórios. O objetivo deste estudo foi avaliar se o perfil farmacocinético combinado da finasterida e da doxazosina não foi significativamente alterado quando esses agentes foram coadministrados, em comparação com seu uso como agentes isolados. Esse foi um estudo comparativo cruzado, randomizado, de 6 sequências e 3 períodos, de três medicamentos: finasterida (5 mg), doxazosina (2 mg) (referências) e a combinação fixa contendo 5 mg de finasterida e 2 mg de doxazosina em um único comprimido (teste). As amostras de plasma obtidas de 30 indivíduos elegíveis foram analisadas simultaneamente para finasterida e doxazosina por HPLC acoplado a um LC-MS/MS com acetato de ciproterona e terazosina como padrões internos. A análise estatística não mostrou diferenças significativas para AUC0-72h (finasterida: 245,3±87,8 vs. teste: 240,5±93,1 e doxazosina: 183,0±42,9 vs. teste: 188,8±45,6 ng.h.mL-1), AUC0-∞ (finasterida: 247,4±92,1 vs. teste: 40,47±93,1 e doxazosina: 190,3±44,3 vs. teste: 188,8±45,6 ng.h.mL-1), e Cmax (finasterida: 34,2±7,1 vs. teste: 29,9±6,2 e doxazosina: 16,3±3,6 vs. teste: 14,9±3,3 ng/mL). As proporções médias de

AUC0-72h/AUC0-∞ para finasterida e doxazosina foram de 99,99% e 99,98%, respectivamente, indicando que o tempo de amostragem foi adequado para ambos os medicamentos. Em resumo, o estudo farmacocinético atual demonstrou bioequivalência entre os agentes individuais e os agentes correspondentes em combinação e forneceu mais evidências da ausência de interação farmacocinética entre a finasterida e a doxazosina.

Palavras-chave: Doxazosina, Finasterida, farmacocinética, hiperplasia prostática benigna, equivalência terapêutica, bioequivalência.

1 INTRODUCTION

Benign prostatic hyperplasia (BPH), affects many older men around the world. It is a non-malignant enlargement of the prostate that may cause urinary symptoms of sufficient severity to interfere with the quality of life of up to 25% of men aged 50-65 [1]. The incidence of BPH increases with age, and prostate enlargement is present in nearly 90% of men by the age of 85 years. The symptoms of enlarged prostate are straining, urgency, frequency, weak stream, and incomplete voiding, and their bladder outlet can be chronically obstructed and lead to acute urinary retention and the need for surgical procedures [2, 3].

Pharmacological therapy for BPH has progressively changed the management of this condition along the past two decades. Two classes of agents have been used with greater success and are now routinely indicated for patients with BPH: 5-alpha-reductase inhibitors and alpha-blockers [4, 5]. The agents representing these classes that are most commonly used in clinical practice are finasteride and doxazosin, respectively, and they may be employed alone or in combination [6]. Randomized clinical trials conducted to date have shown that combination therapy with finasteride and doxazosin is superior to finasteride alone or placebo [7]. However, decreased patient compliance may lead to therapeutic results that less than satisfactory, and interventions focused on improving adherence in patients with BPH are needed [8]. The co-administration of finasteride and doxazosin in a single tablet could thus improve patient compliance assuring that both effective agents are delivered. The aim of this study was to assess whether the combined pharmacokinetic profile for both finasteride and doxazosin was not significantly altered when these agents were co-administered, in comparison with their use as single agents.

2 METHODS

2.1 STUDY DESIGN AND SUBJECT ELIGIBILITY

This was a randomized 3x6 (6 sequences and 3 periods), crossover, comparative study of three medications: finasteride, doxazosin, and the fixed combination of finasteride and doxazosin. Commercially available finasteride tablets (Proscar 5 mg. Merck Sharp & Dohme. Campinas, SP, Brazil) and doxazosin mesylate 2 mg, generic (Merck Brazil. Jacarepagua, RJ, Brazil) were used. The fixed combination, provided by Eurofarma Laboratórios S.A. São Paulo, SP, Brazil contained 5 mg of finasteride and 2 mg of doxazosin in a single tablet. All medications were administered orally under fasting condition to eligible male healthy volunteers, who received all the three treatments in alternated fashion. For each of the medications tested sequentially following the three periods and six sequences, a single dose was administered with water, around 7:00 AM, and subjects remained in the hospital from the preceding night until 24 h after dosing. In addition, subjects returned for blood collection 48 and 72 h after dosing. There was a washout period of at least nine days between the administrations of each of the three medications.

The clinical and statistical phases of the study were conducted at Cebio, in Belo Horizonte, and the analytical phase was conducted at Magabi Bioequivalence Center, in São Paulo, both Brazil.

The study was conducted in accordance with good clinical, laboratory and statistical practice guidelines and Brazilian regulations regarding the study of human subjects, all of whom signed an informed consent form.

Eligible subjects were aged between 18 and 50 years, nonsmokers or former smokers who quit for more than 1 year, with weight 50 kg and over and a body mass index (BMI) between 20 and 27 kg/m^2, with negative serum tests for HIV-1, HIV-2, hepatitis B, and hepatitis C viruses, normal values for hemoglobin, with leukocyte and platelet counts within the normal range, normal urinalysis, and normal serum levels of creatinine, urea, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubins, fasting glucose, and cholesterol. The main exclusion criteria were a history of allergy to finasteride, doxazosin, or related drugs, any evidence of organ dysfunction, a history of gastrointestinal, hepatic, renal, cardiovascular, pulmonary, neurological, psychiatric, or hematological disease, diabetes or glaucoma, a history of psychotropic drug use or alcohol abuse (more than two units of alcohol per day, one unit being equivalent to one glass of beer or wine or a shot of spirits), use of substances metabolized by hepatic microsomal cytochrome P-450 within 30 days preceding the study, participation in

a clinical trial within 6 months, recent (less than three months) blood donation, or absence of adequate venous access.

2.2 BLOOD COLLECTION AND ANALYSIS

Blood samples were colected at time 0 (before drug administration) and at 0.33, 0.67, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 48.0, and 72.0 h after drug administration. The samples were centrifuged at 3500 rpm for 30 min at 4º C, and the plasma was separated and stored at -20º C until analysis.

2.3 SAMPLE ANALYSIS

Briefly, the plasma samples were analyzed simultaneously for finasteride and doxazosin using high performance liquid chromatography coupled to a triple quadrupole mass spectrometer (LC-MS/MS) [9-13]. Atmospheric pressure photoionization (APPI) detection (positive ion mode) was used to ionize the analytes and the internal standards cyproterone acetate and terazosin. The extraction of the samples was done by protein precipitation using cold methanol. The chromatographic conditions for the analytical used a Phenomenex Synergi, Polar RP, 4 µm (4.6 x 50 mm id) column at 1.0 mL/min and as mobile phase an isocratic mixture of methanol/water (90/10; v/v) with 1 mM ammonium acetate. The dopant for the APPI source used was toluene at 0.2 mL/min. The injection volume was 10 uL and the total run time was 2.5 min. The retention times for each analyte were 0.95 min (for finasteride), 1.37 min (for cyproterone acetate), 1.36 min (for doxazosin) and 1.17 min (for terazosin).

The mass spectrometer (AB Sciex model API5000) was equipped with an atmospheric photoionization source run in positive mode (APPI+), and set up in Multiple Reaction Monitoring (MRM), monitoring the transitions 373.4 > 305.2, 417.4 > 357.1, 452.0 > 344.1 and 388.4 > 247.1 for finasteride, cyproterone acetate, doxazosin, and terazosin, respectively. The dwell time was 100 ms and the source temperature was 340º C. Data acquisition and analysis were performed using the software Analyst (v 1.4.2). Conditions were similar to previous published works [9-13].

2.4 PHARMACOKINETIC ANALYSIS

Values for peak plasma concentration (C_{max}) and the time to reach C_{max} (T_{max}) were taken directly from the observed concentration-time profiles. The area under the plasma concentration versus time curve (AUC) from 0 to the last measurable concentration (AUC_{0-t}) was calculated with the linear trapezoidal rule. The AUC from 0 to infinity ($AUC_{0-\infty}$), was

calculated as $AUC_{0-t} + C_t/K_e$, where C_t is the last measurable concentration and K_e is the elimination rate constant.

2.5 STATISTICAL ANALYSIS

For the purpose of relative bioavailability analyses among the three medications, AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were considered as primary variables. The bioequivalence of the same components present in two formulations was assessed by means of analysis of variance and calculating standard 90% confidence intervals (CI) for the ratio test/reference using log-transformed data for C_{max} and AUC_{0-t}. Each component of the combination was considered bioequivalent to the single-agent medication if the confidence interval for the ratio of the means lies within the interval (0.80, 1.25), or equivalently the 90% confidence interval for the difference in the means on the natural log scale are within the interval (-0.2231, 0.2231).

The Phoenix™ WinNonlin® software (Pharsight, Mountain View, CA, USA) was used for statistical analysis.

3 RESULTS

3.1 CHARACTERISTICS OF THE SUBJECTS

Thirty eligible healthy male volunteers were enrolled in the study. Four volunteers dropped out of the study for the following reasons: one was withdrawn because of vomiting that occurred after administration during the third period and three did not show up for outpatient blood collection. The ages of subjects ranged from 20 to 38 years, and their BMI ranged from 20.6 to 27.2 kg/m^2.

3.2 PHARMACOKINETIC RESULTS

The bioanalytical method used for quantifying simultaneously finasteride and doxazosin in human plasma proved to be fast, accurate and sensitive. The LC-MS/MS method presented a lower limit of quantification (LLOQ) of 0.50 ng/mL for finasteride and 0.25 ng/mL for doxazosin. The concentration range for the calibration curves showed to be linear for both analytes from 0.50 to 60.00 ng/mL for finasteride and from 0.25 to 30.00 ng/mL, for doxazosin with $r>0.99$.

The bioanalytical method was validated for precision, accuracy, recovery, specificity/selectivity and biological matrix stability for each analyte. Table 4 summarizes all the results for the pre-study validation. All the results were in accordance to the international Bioanalytical Method Validation (BMV) guidelines including ANVISA's guides [14, 15].

Table 4. Results obtained from the pre-study analytical validation tests.

Assessment		Finasteride	Doxazosin
Specificity/Selectivity	6 different sources	Not significant interference	Not significant interference
Recovery (%)	3 levels (low, medium and high)	103.8 - 112.1	106.3 - 114.8
Precision (CV%)	within batch	1.2 - 5.0	0.8 - 6.0
	between batch	2.4 - 5.6	1.9 - 5.1
Accuracy (%)	within batch	91.7 - 100.4	97.0 - 105.7
	between batch	96.0 - 96.6	100.9 - 105.7
Stability test	Post-processing	35 h (RT)	
	Freeze-and-thaw	3 cycles (-20º C)	
	Short-term	17 h (RT)	
	Long-term	17 d (-20º C)	

RT: room temperature

The mean and standard deviation (SD) plasma pharmacokinetic measures obtained after oral administration of a single dose of both reference and test formulations of each medication in fasting conditions are presented in Table 1. The mean plasma concentrations of finasteride and doxazosin are shown in Figures 1 and 2, respectively.

Figure 1. Mean plasma concentrations obtained after oral administration of single-agent finasteride (reference) and finasteride in the combination (test), in 26 volunteers (error bars represent standard errors of the mean).

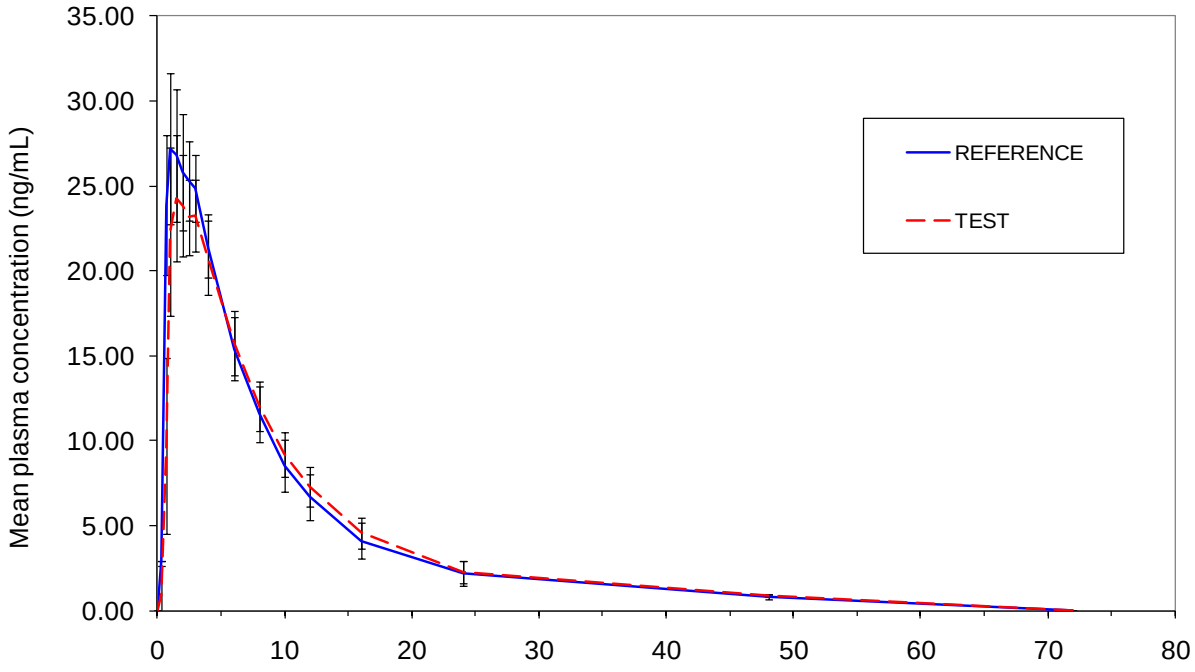

Figure 2. Mean plasma concentrations obtained after oral administration of single-agent doxazosin (reference) and doxazosin in the combination (test), in 26 volunteers (error bars represent standard errors of the mean).

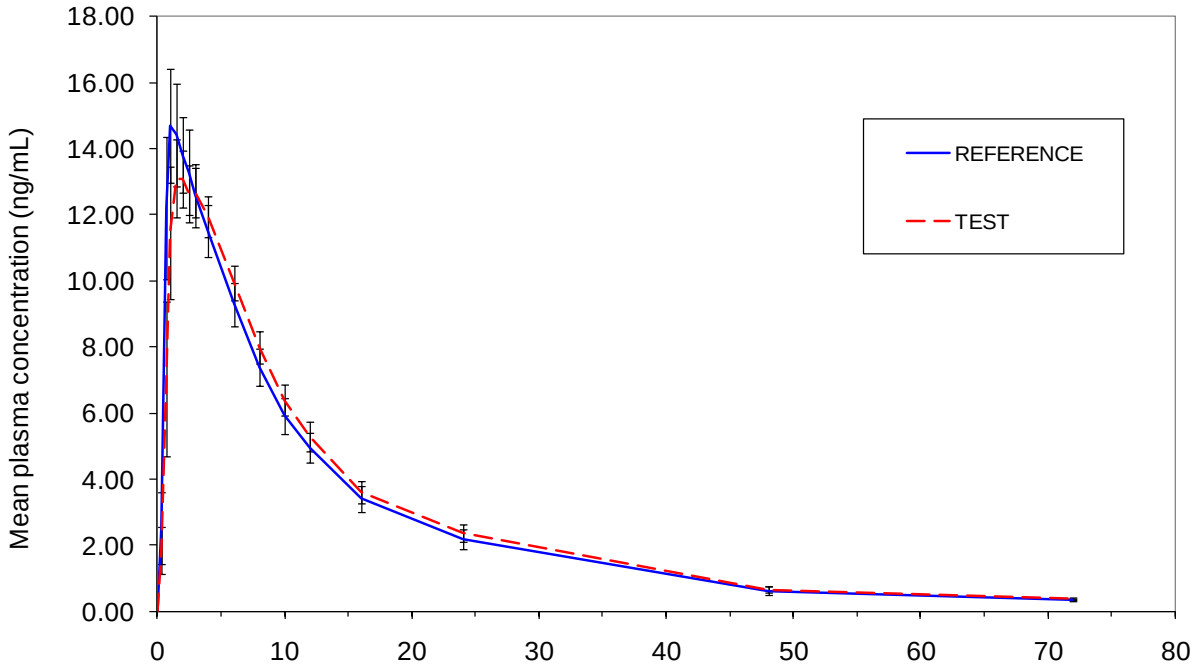

Table 1. Statistics for pharmacokinetics measures of finasteride and doxazosin for both reference and test formulations after oral administration under fasting conditions.

Pharmacokinetic measure	Finasteride		Doxazosin	
	Reference Mean (±SD)	Test Mean (±SD)	Reference Mean (±SD)	Test Mean (±SD)
$AUC_{0\text{-}72h}$ (ng.h.mL^{-1})	245.3±87.8	240.5±93.1	183.0±42.9	188.8±45.6
$AUC_{0\text{-}\infty}$ (ng.h.mL^{-1})	247.4±92.1	240.47±93.1	190.3±44.3	188.8±45.6
C_{max} (ng/mL)	34.2±7.1	29.9±6.2	16.3±3.6	14.9±3.3
T_{max} (h)	1.8±1.2	2.1±1.4	1.4±0.6	2.4±1.4
$t_{½}$ (h)	6.0±2.1	6.5±2.7	11.5±2.4	12.3±2.6

SD: standard deviation

Tables 2 (for finasteride) and 3 (for doxazosin) present the ratios (test/reference) and respective 90% confidence intervals (CIs) for bioequivalence analysis regarding $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$ and C_{max} (log-transformed data). The statistical analysis showed no significant differences for the $AUC_{0\text{-}72h}$, $AUC_{0\text{-}\infty}$, and C_{max} between the single agents and corresponding agents in the combinations, thus demonstrating bioequivalence according to the criteria utilized (90% CIs within 0.80 and 0.125). The mean ratios of $AUC_{0\text{-}72h}/AUC_{0\text{-}\infty}$ for finasteride and doxazosin were 99.99% and 99.98%, respectively, indicating that the sampling time was adequate for both drugs.

Table 2. Results for pharmacokinetic measures obtained after oral administration of both reference and test formulations of finasteride 5 mg.

Pharmacokinetic measure	Mean ratio	90% Confidence interval
log $AUC_{0\text{-}72h}$ (ng.h/mL)	0.98	0.92-1.04
log $AUC_{0\text{-}\infty}$ (ng.h/mL)	0.97	0.97-1.07
log C_{max} (ng/mL)	0.88	0.81-0.95

Table 3. Results for pharmacokinetic measures obtained after oral administration of both reference and test formulations of doxazosin 2 mg.

Pharmacokinetic measure	Mean ratio	90% confidence interval
log $AUC_{0\text{-}72h}$ (ng.h/mL)	1.03	0.98-1.08
log $AUC_{0\text{-}\infty}$ (ng.h/mL)	0.99	0.94-1.04
log C_{max} (ng/mL)	0.91	0.86-0.97

4 DISCUSSION

The current study shows that finasteride and doxazosin formulated in a single tablet display a pharmacokinetic behavior very similar to that of these same agents administered individually after single dosing. The results presented suggest that this combination is a valid approach towards facilitating drug administration and increasing patient compliance in the treatment of men with BPH who require both finasteride and doxazosin for symptom relief. The available data suggest that combination finasteride and doxazosin therapy is beneficial in the treatment of BPH and the associated symptoms. The greatest efficacy was evident in patients with an enlarged prostate, more severe symptoms, and higher prostate-specific antigen (PSA) levels [6].

To our knowledge, this is the first published study investigating the pharmacokinetics of this combination in a single formulation. As a matter of fact, only one study published to date has assessed the pharmacokinetic behavior of finasteride and doxazosin after co-administration of these agents [16]. In that study, however, the agents were administered in separate tablets, and the authors found no statistically significant pharmacokinetic interaction between finasteride and doxazosin. On the other hand, a statistically significant interaction was noted between finasteride and terazosin, another alpha-blocker that may be used to treat patients with BPH.

From the bioanalytical perspective, although one can find several methods addressing the quantification of either doxazosin [17] or finasteride [18] in human plasma, none of them were developed, validated and used for simultaneous determination of both compounds. The bioanalytical herein presented is fast (2.5 min per sample), simple for sample preparation (protein precipitation) and it showed good sensitivity for PK studies.

As a 5-alpha-redutase inhibitor, finasteride blocks the conversion of testosterone to dihydrotestosterone, thus reducing prostate size. Doxazosin is an alpha-blocker, thus being able to induce smooth-muscle relaxation in the prostate and bladder neck and reduce the clinical symptoms of BPH. Their combined use is therefore based on solid rationale. From a clinical standpoint, data from the Medical Therapy of Prostatic Symptoms (MTOPS) study, a randomized trial of finasteride, doxazosin, or the combination, suggested a role for long-term use of the combination, especially in patients with greater symptom severity [as indicated by a higher score on the American Urological Association symptom index [19, 20], larger prostate volume, and higher PSA levels at baseline [7].

In the MTOPS study, combination therapy with doxazosin and finasteride was significantly more effective than either component alone, both for symptom control and for reducing the rate of overall clinical progression of BPH. In contrast, trials of shorter duration had failed to demonstrate a benefit for the combined use of a 5-alpha-redutase inhibitor and finasteride [21, 22].

Patient compliance with self-administered oral medication is a universal problem in clinical medicine. Compliance rates for patients with chronic disorders are generally estimated to be approximately 50%, and may be as low as 30% for certain conditions [23]. Among patients with BPH, a study using California Medicaid data on 2.640 adult males with one or more diagnoses and two or more prescription fills for BPH found compliance rates of 40% to any medication, with a significantly greater proportion for finasteride than for doxazosin or other alpha-blockers, as well as for those using single as opposed to multiple medications [8]. Thus, for patients requiring therapy with both finasteride and doxazosin, low compliance rates should be expected in clinical practice. The use of both agents in a single tablet might increase compliance, and we believe this hypothesis should be tested in future trials among patients with BPH.

The current study is limited by the fact that a control group composed of subjects treated with both agents has not been assessed, as the goal of pharmacokinetic assessment in this case was to investigate the bioequivalence of the combination and each individual agent, as requested by Brazilian health authorities. On the other hand, the lack of pharmacokinetic interaction between finasteride and doxazosin, as demonstrated by Vashi et al., 1998 [16] suggests that this control group would not provide additional information regarding the bioequivalence of the combination.

In summary, the current pharmacokinetic study provides further evidence for the lack of pharmacokinetic interaction between finasteride and doxazosin, at the same time suggesting

that their combined use in a single tablet should lead to clinical results comparable to those seen when these two agents were administered separately.

Furthermore, the LC-MS-MS method described here for drug quantification showed to be high sensitivity, specificity and high samples throughput required for pharmacokinetic studies.

REFERENCES

1. Thorpe A, Neal D. Benign prostatic hyperplasia. Lancet. 2003;361(9366):1359-67.

2. Naslund MJ, Miner M. A review of the clinical efficacy and safety of 5alpha-reductase inhibitors for the enlarged prostate. Clin Ther. 2007;29(1):17-25.

3. O'Leary MP. Lower urinary tract symptoms/benign prostatic hyperplasia: maintaining symptom control and reducing complications. Urology. 2003;62(3 Suppl 1):15-23.

4. Tacklind J, Fink HA, Macdonald R, Rutks I, Wilt TJ. Finasteride for benign prostatic hyperplasia. Cochrane Database Syst Rev. 2010(10):CD006015.

5. MacDonald R, Wilt TJ, Howe RW. Doxazosin for treating lower urinary tract symptoms compatible with benign prostatic obstruction: a systematic review of efficacy and adverse effects. BJU Int. 2004;94(9):1263-70.

6. McVary KT. A review of combination therapy in patients with benign prostatic hyperplasia. Clin Ther. 2007;29(3):387-98.

7. Bautista OM, Kusek JW, Nyberg LM, McConnell JD, Bain RP, et al. Study design of the Medical Therapy of Prostatic Symptoms (MTOPS) trial. Control Clin Trials. 2003;24(2):224-43.

8. Nichol MB, Knight TK, Wu J, Barron R, Penson DF. Evaluating use patterns of and adherence to medications for benign prostatic hyperplasia. J Urol. 2009;181(5):2214-21; discussion 21-2.

9. Al-Dirbashi OY, Aboul-Enein HY, Jacob M, Al-Qahtani K, Rashed MS. UPLC-MS/MS determination of doxazosine in human plasma. Anal Bioanal Chem. 2006;385(8):1439-43.

10. Phapale PB, Lee HW, Lim MS, Kim EH, Kim SD, et al. Rapid determination of finasteride in human plasma by UPLC-MS/MS and its application to clinical pharmacokinetic study. J Chromatogr B Analyt Technol Biomed Life Sci. 2010;878(20):1718-23.

11. Chen L, Jiang X, Huang L, Lan K, Wang H, et al. Bioequivalence of a single 10-mg dose of finasteride 5-mg oral disintegrating tablets and standard tablets in healthy adult male Han Chinese volunteers: a randomized sequence, open-label, two-way crossover study. Clin Ther. 2009;31(10):2242-8.

12. Chytil L, Strauch B, Cvacka J, Maresova V, Widimsky J, Jr., et al. Determination of doxazosin and verapamil in human serum by fast LC-MS/MS: application to document non-compliance of patients. J Chromatogr B Analyt Technol Biomed Life Sci. 2010;878(30):3167-73.

13. Erceg M, Cindric M, Pozaic Frketic L, Vertzoni M, Cetina-Cizmek B, et al. A LC-MS-MS method for determination of low doxazosin concentrations in plasma after oral administration to dogs. J Chromatogr Sci. 2010;48(2):114-9.

14. RESOLUÇÃO-RE nº 1.170, DE 19 DE ABRIL DE 2006, (2006).

15. RESOLUÇÃO-RE Nº 899, DE 29 DE MAIO DE 2003, (2003).

16. Vashi V, Chung M, Hilbert J, Lawrence V, Phillips K. Pharmacokinetic interaction between finasteride and terazosin, but not finasteride and doxazosin. J Clin Pharmacol. 1998;38(11):1072-6.

17. Chung M, Vashi V, Puente J, Sweeney M, Meredith P. Clinical pharmacokinetics of doxazosin in a controlled-release gastrointestinal therapeutic system (GITS) formulation. Br J Clin Pharmacol. 1999;48(5):678-87.

18. de Menezes FG, Ribeiro W, Ifa DR, de Moraes ME, de Moraes MO, et al. Bioequivalence study of finasteride. Determination in human plasma by high-pressure liquid chromatography coupled to tandem mass spectrometry. Arzneimittelforschung. 2001;51(2):145-50.

19. Barry MJ, Fowler FJ, Jr., O'Leary MP, Bruskewitz RC, Holtgrewe HL, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. J Urol. 1992;148(5):1549-57; discussion 64.

20. Barry MJ, Williford WO, Fowler FJ, Jr., Jones KM, Lepor H. Filling and voiding symptoms in the American Urological Association symptom index: the value of their distinction in a Veterans Affairs randomized trial of medical therapy in men with a clinical diagnosis of benign prostatic hyperplasia. J Urol. 2000;164(5):1559-64.

21. Lepor H, Williford WO, Barry MJ, Brawer MK, Dixon CM, et al. The efficacy of terazosin, finasteride, or both in benign prostatic hyperplasia. Veterans Affairs Cooperative Studies Benign Prostatic Hyperplasia Study Group. N Engl J Med. 1996;335(8):533-9.

22. Kirby RS, Roehrborn C, Boyle P, Bartsch G, Jardin A, et al. Efficacy and tolerability of doxazosin and finasteride, alone or in combination, in treatment of symptomatic benign prostatic hyperplasia: the Prospective European Doxazosin and Combination Therapy (PREDICT) trial. Urology. 2003;61(1):119-26.

23. Kane SV. Systematic review: adherence issues in the treatment of ulcerative colitis. Aliment Pharmacol Ther. 2006;23(5):577-85.