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Combining benefits of an adrenergic and a muscarinic blocker in a single formulation – A pharmacokinetic evaluation

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ABSTRACT

A pharmacokinetic bioequivalence study was conducted in Asian subjects, to compare a fixed dose combination capsule single oral dose of alpha adrenoceptor blocker—Alfuzosin hydrochloride 10 mg extended release and muscarinic antagonists—Solifenacin succinate 5 mg against individually administered Xatral XL 10 mg tablets (Alfuzosin) of Sanofi Synthelabo Limited, United Kingdom (UK) and Vesicare 5 mg tablets (Solifenacin) of Astellas Pharma Limited, UK under fed conditions. Blood samples were collected pre-dose up to 72 h post dose for determination of plasma Alfuzosin and Solifenacin concentrations and calculation of the pharmacokinetic parameters. ANOVA was performed on the log (natural)-transformed pharmacokinetic parameters. A 90% confidence interval for the ratios of the test and reference product averages (least square means) were calculated for alfuzosin and solifenacin. The 90% confidence intervals obtained for alfuzosin for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were 102.74–122.75%, 95.84–116.96% and 95.82–116.76%, respectively. The 90% confidence intervals obtained for Solifenacin for C_{max}, and AUC_{0-72} were 89.55–97.91% and 90.47–99.38%, respectively. Based on the results, the fixed dose combination was concluded to be bioequivalent to individually administered products.

1. Introduction

Benign prostatic hyperplasia (BPH) is a disorder that is manifested as an enlargement of the prostate gland and caused by the progressive hyperplasia of stromal and glandular prostatic cells. This growth is nonmalignant; however, it ultimately leads to constriction of the urethral opening. Consequently, clinical BPH is often associated with lower urinary tract symptoms (LUTS). In ageing men, BPH is considered the main cause of LUTS (Miller and Tarter, 2009; Lepor, 2005; Speakman, 2008). BPH has been diagnosed in about fifty percent of males over the age of 50 and ninety percent of males over the age of 80. The medical therapies used for treatment of BPH are targeted to diminishing bladder outlet obstruction in order to reduce prostate volume and relax prostate smooth muscle tension (Sugaya et al., 2009). Alpha-adrenergic antagonists (alpha-blockers), 5-alpha-reductase Inhibitors (5-ARIs) and anticholinergic agents are the mainstay of pharmacotherapy of LUTS/BPH. Surgery and complementary medicine are the alternatives (American Urological Association, 2010).

Overactive bladder (OAB) is a symptom complex manifested as urinary urgency, leading to increased urinary frequency and nocturia, often with urgency incontinence. Of the men over 18 who experience LUTS, about 49% present with symptoms of OAB. Symptoms, such as bladder outlet obstruction (BOO) and detrussor overactivity (DO), overlap in BPH and OAB. Thus, both OAB and BPH may present as LUTS (Chen, 2008). In 50% to 75% of patients with LUTS/BPH, OAB is also present (Seo et al., 2011). Bladder contractions are mediated by acetylcholine, specifically *via* M_2 and M_3 receptors. Anticholinergic agent like Solifenacin is used to reduce bladder smooth muscle contractility. Due to these reasons, administration of alpha-adrenergic blockers in combination with anticholineric agents could be beneficial.

Alfuzosin, an alpha-adrenergic antagonist has been in clinical use for more than three decades. The drug has a better adverse event profile as compared to other alpha-adrenergic antagonists of its class. In terms of efficacy, there is little difference among the alpha-adrenergic antagonists. Alfuzosin is metabolized extensively in the liver to form inactive metabolites which are mostly excreted in the faeces. CYP3A4 has been identified to be the major metabolizing enzyme. It has a plasma half-life of 7 h (immediate release formulation) and a clearance of 0.36 L/h/kg. The pharmacokinetics are unchanged in cardiac insufficiency, though the prolonged release formulation is contra-indicated in patients with hepatic insufficiency.

Solifenacin, an anticholinergic agent, has been widely used to treat OAB. It is considered to be more specific for the bladder among older anticholinergic agents. It is metabolized primarily in

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the liver, mediated by CYP3A4 and to a lesser extent, CYP1A1 and CYP1A2 (Doroshyenko and Fuhr, 2009). The plasma half-life is 45 to 68 h. Solifenacin at therapeutic dosage does not appear to inhibit liver cytochrome P450 isoenzymes and therefore is unlikely to cause pharmacokinetic drug-drug interactions based on CYP dependent metabolism of co-administered drugs (Basra and Kelleher, 2008). There are no pharmacokinetic interactions reported between alfuzosin and solifenacin.

In patients presenting with symptoms of OAB and LUTS/BPH, a combination of alpha-adrenergic antagonists and anticholinergic agents could be beneficial (Chen, 2008). Hence, fixed dose combination (FDC) of alpha-adrenergic and anticholinergic agent (given once daily) is an attractive option for patients of BPH/LUTS with OAB. FDCs offer a strategy to reduce the pill burden for patients and a simple, more convenient way of managing their medicines. FDCs often yield better clinical outcomes compared with combinations of the same drugs given separately.

A fixed dose combination of Alfuzosin and Solifenacin has been developed for patients with LUTS/BPH alongside OAB. The pharmacokinetic parameters of Alfuzosin and Solifenacin were compared to establish bioequivalence between the fixed dose combination tablet of Alfuzosin Hydrochloride 10 mg Extended Release and Solifenacin Succinate 5 mg, and Xatral XL 10 mg tablets (containing alfuzosin hydrochloride prolonged release 10 mg) of Sanofi-Synthelabo Limited, United Kingdom (UK) and Vesicare 5 mg tablets (containing solifenacin succinate 5 mg) of Astellas Pharma Limited, UK administered concurrently. The study was conducted in healthy adult human subjects under fed conditions. The pharmacokinetic and safety results of the bioequivalence study are presented in this paper.

2. Materials and methods

2.1. Study design

The study was conducted as open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, crossover, bioequivalence study comparing fixed dose combination of Alfuzosin Hydrochloride 10 mg Extended Release and Solifenacin Succinate in 42 healthy, adult, male, human volunteers under fed condition. Subjects served as their own control in this study.

2.2. Subjects

A total of forty-two (42) male subjects of Asian origin, in the age range of 18–45 years were enrolled into the study. Each subject gave written informed consent before participation in the study. The study protocol and informed consent form were reviewed and approved by an independent ethics committee (Sentinel Independent Ethics Committee). This research was carried out in accordance to the basic principles defined in European Union Directive 2001/20/EC, the ICH 'Guidance for Good Clinical Practice', ICMR 'Ethical Guidelines for Biomedical Research on Human Participants (2006)', CDSCO 'Guidance on Good Clinical Practices for Clinical Research in India' and the principles enunciated in the Declaration of Helsinki (WMA General Assembly, Seoul 2008).

All subjects were healthy according to medical history, based on the demographic data (including age, sex, history of smoking and alcohol consumption, body weight and height, BMI), vital signs and physical examination, ECG, chest X-ray and clinical laboratory tests (including disease markers of syphilis, HIV and hepatitis B and C). No drug was allowed for at least two weeks before initiation of study and until completion of the study. Tests for alcohol, benzodiazepines, amphetamine, cocaine, opiates and tetra-hydro cannabinoid were performed at check-in of all periods.

2.3. Drug treatment

A single oral dose of treatment 1 (T) – test (FDC capsule of Alfuzosin Hydrochloride 10 mg Extended Release and Solifenacin Succinate 5 mg of Ranbaxy Laboratories Limited, India) or treatment 2 (R) – reference [co-administration of Xatral® XL 10 mg tablets (containing Alfuzosin hydrochloride prolonged release 10 mg) of Sanofi Synthelabo Limited, United Kingdom and Vesicare® 5 mg tablets (containing solifenacin succinate 5 mg) of Astellas Pharma Limited, United Kingdom] was administered during each period of the study along with 240 mL of drinking water, under the supervision of trained study personnel. A breakfast was served after an overnight fast of at least 10 h. Subjects received the study drug at least 15 min after consumption of a high-fat high-calorie breakfast. During both periods of the study, allocation of subjects to the test and reference treatments was done as per the randomization schedule generated by SAS software (using a random element) to reduce bias. Study formulations were dispensed into labeled paper pouches, which were kept inside labeled zip lock plastic pouches. The two treatments were separated by a washout period of thirty-seven (37) days.

2.4. Blood sample collection

A total of sixty-four (64) (including two pre-dose duplicate samples), 6 mL blood samples were collected and transferred to pre-chilled CPDA Vacuette in wet ice bath during the course of the study from each subject. Blood samples were collected at pre-dose and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0, 11.0, 12.0, 16.0, 20.0, 24.0, 30.0, 36.0, 42.0, 48.0, 60.0 and 72.0 h post-dose in each period. After blood sample collection, plasma was separated by centrifugation and aliquoted in duplicate into pre-labelled polypropylene tubes. Plasma samples were then stored below −15 °C until transfer to the bioanalytical section for assay. Stability of all analytes under these storage conditions was demonstrated during method validation.

2.5. Analytical method

The plasma levels of alfuzosin and solifenacin were determined using a validated simultaneous bio-analytical LC–MS/MS method, using alfuzosin-D3 and doxazosin as internal standards. Analytes and internal standards were detected by tandem mass spectrometric (MS/MS) method using multiple reaction monitoring. Sample preparation process was accomplished by positive-pressure solid phase extraction. The processed sample was chromatographed and analyzed on Supelco Discovery C_8, 100 × 4.6 mm, 5 μm column using Acetonitrile: Methanol: 5 mM Ammonium formate solution: Formic acid – 40: 50: 10: 0.1% v/v/v/v as mobile phase. Alfuzosin and Solifenacin were chromatographed and analyzed by MS detector. Signals from the detector were captured in a computer and processed using Analyst software. The limit of quantitation was 74.7 pg/mL and 50.6 pg/mL for Alfuzosin and Solifenacin, respectively. The calibration was shown to be linear from 74.7 pg/mL to 22651.0 pg/mL, for Alfuzosin and from 50.6 pg/mL to 15333.0 pg/mL for Solifenacin.

The between batch accuracy using internal standard area ratio method ranged from 94.6% to 106.3% for Alfuzosin and from 90.6% to 104.8% for Solifenacin. The between batch precision using internal standard area ratio method ranged from 2.9% to 8.9% for Alfuzosin and from 3.9% to 8.7% for Solifenacin.