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Study of pharmacokinetic interaction of paroxetine and roxithromycin on bencycloquidium bromide in healthy subjects ☆

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ABSTRACT

Purpose: The aim of this study was to investigate the potential drug–drug interaction between Bencycloquidium bromide (BCQB) and paroxetine, and between BCQB and roxithromycin.
Methods: Two studies were conducted on healthy male Chinese volunteers. Study A was an open-label, two-period, one-sequence crossover study ($n = 21$). Each participant received a single nasal spray dose of BCQB 180 μg on day 1. After a 7-day wash-out period, subjects received 20 mg of paroxetine from day 8 to 17, and were co-administered 20 mg of paroxetine and BCQB 180 μg on day 18. In study B, participants ($n = 12$) were randomly assigned to two groups. In period I, group A received BCQB 180 μg on day 1, followed by the same dose four times daily from day 4 to 10, then, on day 11 a single dose of 150 mg roxithromycin with BCQB 180 μg were co-administered. In parallel, group B received a single dose of roxithromycin 150 mg on day 1, followed by 300 mg of roxithromycin from day 4 to 10, then, on day 11 a single dose of BCQB 180 μg with roxithromycin 300 mg were co-administered. After a wash-out time of 7 days the respective treatments of each group (A and B) were swapped in period II. Blood samples were collected for pharmacokinetic analysis. Statistical comparison of pharmacokinetic parameters was performed to identify a possible drug interaction between treatments. Tolerability was evaluated by recording adverse events.
Results: Study A: Geometric mean AUC_{0-36} for BCQB alone and co-administered with paroxetine were 474.3 and 631.3 pg h/ml, respectively. The geometric mean ratio (GMR) of AUC_{0-36} was 1.33 (1.13–1.46), 90% C.Is, and was out the predefined bioequivalence interval (90% C.Is, 0.80–1.25). Geometric mean C_{max} were 187.0 and 181.2 pg/ml. Study B: The GMR of AUC_{0-36} was 0.98 (0.90–1.07), 90% C.Is for BCQB, and the GMR of AUC_{0-72} was 0.98 (0.87–1.11), 90% C.Is for roxithromycin. Both GMRs were within the predefined bioequivalence interval (90% C.Is, 0.80–1.25). Other pharmacokinetic parameters were within the predefined interval. No serious adverse events were reported and no significant clinical changes were observed in laboratory test results, vital signs and ECGs in any of the studies. All treatments were well tolerated.
Conclusion: The co-administration of BCQB with paroxetine showed a moderate increase in BCQB exposure, but was not clinically relevant. Also, no drug interaction was found between BCQB and roxithromycin.

1. Introduction

Upper respiratory infections, such as rhinitis, asthma and chronic obstructive pulmonary disease (COPD), are troublesome and life threatening diseases which greatly affect the quality of life of people. It is estimated to affect about 10–40% of the global population with an increasing prevalence in both children and adults (Wallace et al., 2008). For instance, COPD is a major cause of morbidity and mortality worldwide (Varkey and Varkey, 2008). Upon simultaneous exposure to both allergic inflammation and viral infections, individuals who develop asthma with COPD-like inflammation, appear to be poorly responsive to β2-agonists (Kanazawa, 2006). Acetylcholine is the primary parasympathetic neurotransmitter in the airways and an autocrine/paracrine secreted hormone from non-neuronal origins including inflammatory cells and airway structural cells. Acetylcholine is well-known in regulating bronchoconstriction, mucus secretion, inflammatory cell chemotaxis and activation, and also participates in signaling events leading to chronic airway wall remodeling that are associated with

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chronic obstructive airway diseases including asthma and COPD (Kistemaker et al., 2012). Unfortunately, most marketed muscarinic receptor antagonists failed to be selective among muscarinic M1, M2 and M3 receptors causing many severe side effects such as tachycardia and uroschesis (Haddad et al., 1999). Therefore, bencycloquidium bromide (BCQB), a novel selective muscarinic M1/M3 receptor antagonist is developed for the treatment of rhinitis, asthma and COPD with no side effect on cholinergic receptors of the central nerve system and heart (Jiang et al., 2011). A series of studies have shown BCQB to be a potent drug with significant therapeutic effects on hypersensitive rhinitis, allergic rhinitis, airway-inflammation, pruritus and acute rhinitis known as common cold (Cao et al., 2011; Xu et al., 2008; Li et al., 2011). Also, early study of BCQB in human showed its safety and tolerability after single doses escalation and multiple doses escalation (Sun et al., 2012). Our recent study showed that BCQB is metabolized mainly by CYP2D6 and also weekly by CYP3A4/5 and CYP2C19 (Agbokponto et al., 2014).

In clinical practice, β2-agonists or muscarinic receptor antagonists are often used in combination with antibiotics and anti-allergies in the treatment of COPD or rhinitis. It has long been believed that antibiotics have no advantage in treating upper respiratory tract infections (Leyer et al., 2009), yet they are often prescribed with the belief that they may prevent secondary bacterial infections. Health authorities have been strongly encouraging physicians to decrease prescribing antibiotics to treat common upper respiratory tract infections because antibiotic usage does not significantly reduce recovery time for these viral illnesses (Reveiz et al., 2007). However, in certain higher risk patients with underlying lung disease, such as COPD, evidence does exist to support the treatment of bronchitis with antibiotics to shorten the course of the illness and decrease treatment failure (Ram et al., 2006). In addition, previous studies on acute purulent rhinitis and acute clear rhinitis suggested a benefit for antibiotics but their routine use was not recommended (Arroll and Kenealy, 2005). Macrolides are widely used as antibacterial drugs, for which clinical and experimental data indicated that they also modulate inflammatory responses, contributing to the treatment of inflammatory diseases (Culic et al., 2001). Roxithromycin is clinically representative of the most commonly used macrolide antibiotics, especially in China, which is effective in the treatment of upper and lower respiratory tract infections, with fewer interactions and better tolerability when compare to erythromycin or clarithromycin (De Campora et al., 1992; Jeffrey and Richard, 2001; Konno et al., 1994). In addition to its antibacterial function, roxithromycin suppressed the secretion of T cell cytokine interleukins (IL-4, IL-5), reduced ovalbumin-induced Th2 cytokine production and pulmonary eosinophilia expression in lung tissues; similar to BCQB (Asano et al., 2001; Cao et al., 2011). Roxithromycin and its major metabolites have been shown to inhibit the CYP3A-dependent oxidation in human microsomal liver cells and recombinant human P450 systems in vitro (Yamazaki et al., 1996). BCQB is metabolized by CYP2D6 and CYP3A4/5 *in vivo*. Thus, the assessment of drug–drug interaction between BCQB and roxithromycin became relevant. Also, the possibility that BCQB may be co-administered with other drugs such as substrates or inhibitors of CYP2D6 is always present. Therefore, this work, divided into two parts, was designed to assess the potential drug–drug interaction between BCQB and roxithromycin and between BCQB and paroxetine, a strong selective inhibitor of CYP2D6.

2. Participants and methods

The study was conducted at a single center at West China Hospital affiliated to Sichuan University, Chengdu, in China. It was approved by the Ethics Committee at the study center and conducted in accordance with the guidelines of the Declaration of Helsinki and Good Clinical Practice (GCP). The study documents were reviewed by an independent ethics review committee in accordance with local regulations. All subjects provided written informed consent after a comprehensive explanation of the study before any study-related procedures were performed. This study was divided into two parts, the first part investigated the pharmacokinetic interaction between BCQB and paroxetine (study A) and the second part (study B) studied the pharmacokinetic interaction between BCQB and roxithromycin. The design of this work was in compliance with the guidelines for clinical drug interaction studies (Guidance for Industry, 2012; Bjornsson et al., 2003).

2.1. Study population

Study A enrolled twenty-one healthy non-smoking Chinese male volunteers aged between 21 and 40 years, and study B recruited twelve healthy non-smoking Chinese male volunteers aged between 20 and 40 years. Subjects' health states were analyzed on the basis of medical history, physical examinations, ECG and laboratory examinations.

The inclusion criteria for both studies were as follows: healthy volunteers with a normal clinical examination that included medical history, non-smokers, body mass index of 18 to 28 kg/m^2, normal laboratory tests, normal ECG and QTc interval results. The following exclusion criteria were applied to subjects in these clinical trials: (1) history of clinically significant cardiovascular, renal, urinary tract, hepatic, pulmonary, gastrointestinal, eye, mouth, nose, or mucosal diseases that might interfere with absorption, distribution, metabolism, or excretion of BCQB, paroxetine or roxithromycin; (2) history of nervous system or muscular disease, seizure disorder or a psychiatric disorder that might hinder compliance with the study; (3) history of known allergy or intolerance to any of these drugs, history of tobacco, alcohol or drug abuse; (4) those who had received an investigational drug, any known enzyme-inducing/inhibiting agents, donation of blood in the previous 3 months, or had received any drug including herbal/dietary supplements that may affect metabolism of CYP3A and/or CYP2C19 within 2 weeks before the study start date; (5) those with abnormalities in physical examinations, vital signs, ECGs, laboratory test results or considered by the investigator for any reason to be an unsuitable candidate for the study. The screening visit for determination of eligibility was conducted within 30 days prior to admission to the treatment place.

2.2. Study design

2.2.1. Study A

The study was an open-label, two-period, one-sequence cross-over study. Twenty-one healthy subjects were administered nasally a single dose of 180 μg BCQB nasal spray on day 1. After a 7-day wash-out period, subjects were administered orally 20 mg of paroxetine once a day from day 8 to 17. A single dose of 180 μg BCQB was co-administered with 20 mg of paroxetine on day 18. Blood samples were collected on day 1 and day 18 for pharmacokinetics assessment of BCQB. The dose of paroxetine (20 mg) was chosen based on the recommended starting dosage per day and steady state was achieved after 7–8 days in most subjects (Lim et al., 2008; Schoedel et al., 2012).

2.2.2. Study B

This study was an open-label, two-period, two-way, cross-over design. Twelve healthy male volunteers were randomly assigned to two groups (A and B). In period I, group A were given a single dose of BCQB 180 μg on day 1, followed by multiple doses of BCQB