Pulmonary Pharmacology & Therapeutics 26 (2013) 574–580

Contents lists available at SciVerse ScienceDirect

Pulmonary Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/ypupt

Bronchodilation and safety of supratherapeutic doses of salbutamol or ipratropium bromide added to single dose GSK961081 in patients with moderate to severe COPD

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ARTICLE INFO

Article history:
Received 13 January 2013
Received in revised form
7 March 2013
Accepted 12 March 2013

Keywords:
COPD
Bi-functional molecule
Dual pharmacophore
MABA
Salbutamol
Ipratropium bromide
Bronchodilatory effects
GSK961081

ABSTRACT

Background: There are few data on the bronchodilatory effects of adding short-acting bronchodilators (SABA) to maintenance, long-acting bronchodilator therapy. This study assessed the additional bronchodilation and safety of adding supratherapeutic doses of salbutamol (SALB) or ipratropium bromide (IPR) to the novel bi-functional molecule (or dual pharmacophore) GSK961081 400 μg (MABA 400) or 1200 μg (MABA 1200).

Methods: This randomised, double-blind, complete, crossover study in 44 patients with moderate to severe COPD, evaluated 6 treatments with a washout of at least 7 days between treatments: single doses of MABA 400 or MABA 1200 followed by cumulative doses of either SALB (3× 200 μg at 20 min intervals), IPR (20 μg, 20 μg and 40 μg at 20 min intervals) or placebo (PLA) (three doses at 20 min intervals) at 1 h, 12 h and 24 h post-MABA dose. The primary endpoint was maximal increase in FEV_1, from pre-dose bronchodilator (SABA/PLA), measured 15 min after each cumulative dose of SALB, IPR or PLA. Systemic pharmacodynamics (potassium, heart rate, glucose and QTc), adverse events and systemic pharmacokinetics were also assessed.

Results: The additional bronchodilatory effects at 12 h and 24 h for both SALB and IPR were of a similar magnitude and statistically significant relative to PLA; mean differences (SE) (L) following MABA 400 dosing: 0.139 (0.023) after SALB at 12 h; 0.123 (0.022) after SALB at 24 h; 0.124 (0.023) after IPR at 12 h; 0.141 (0.021) after IPR at 24 h; and after MABA 1200 dosing: 0.091 (0.023) after SALB at 12 h; 0.126 (0.022) after SALB at 24 h; 0.055 (0.023) after IPR at 12 h; 0.122 (0.022) after IPR at 24 h. Any additional bronchodilator effects at 1 h were small and not clinically significantly different from PLA. There were small, non-clinically significant increases in mean heart rate after both MABA doses plus SALB, and decreased potassium levels in four patients after MABA 1200 plus SALB (×3) or PLA (×1) were observed but overall all treatments were well tolerated and raised no significant safety signals.

Conclusion: The additional bronchodilation achieved following supratherapeutic doses of SALB and IPR on top of single doses of MABA 400 or 1200 was comparable for the two agents and neither were associated with any clinically relevant systemic pharmacodynamic effects other than the small transient hypokalemic effect in a 3 out of 41 patients receiving additional high dose salbutamol and MABA 1200. Either short-acting bronchodilator could potentially be used as rescue medication on top of MABA therapy.

1. Introduction

It is recommended that treatment of chronic obstructive pulmonary disease (COPD) should be based on an individualised, combined assessment which considers both current disease, determined by assessment of symptoms and activity limitation, and future risk, determined from airflow limitation or exacerbation history [1]. Inhaled bronchodilators are the mainstay of the symptomatic treatment of COPD, and both long-acting β_2-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) are frequently prescribed as maintenance therapy. A combination of these agents can provide greater efficacy for patients who remain symptomatic on a monotherapy with a LABA or LAMA [1,2], and a number of studies have demonstrated a superior bronchodilation effect of combining a LABA with a LAMA compared with the individual agents alone [3–7].

GSK961081 is a novel bi-functional molecule (or dual pharmacophore) which combines muscarinic antagonism (MA) and β_2-agonism (BA) in a single molecule. This approach avoids the

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http://dx.doi.org/10.1016/j.pupt.2013.03.009

complication of combining different drugs in one inhaler, providing a fixed ratio of MA and BA with simplified formulation and pharmacokinetics compared with combination therapy [8]. A key advantage of bi-functional molecules is the potential to provide a simpler route to triple therapy (for example a dual bronchodilator combination with an inhaled corticosteroid), a logical next step for COPD patients with high levels of symptoms and who are at risk of frequent exacerbations.

Pre-clinical data showed GSK961081 to be a potent functional antagonist of muscarinic receptors as well as a potent, selective and full agonist at the β_2-adrenoceptor [9], which produced significant and sustained bronchoprotection that was significantly greater than that with either the MA or BA components alone [10]. Clinically, GSK961081 400 μg and 1200 μg once daily for 2 weeks demonstrated sustained bronchodilation similar to a combination of tiotropium 18 μg once daily plus salmeterol 50 μg twice daily but with a more rapid onset of action, in patients with moderate COPD [11]. A dose-ranging 4 week study in patients with moderate to severe COPD also showed GSK961081 to be an effective bronchodilator [12]. In this study, the optimal total daily dose was 400 μg either given once a day or 200 μg given twice a day, resulting in an improvement in day 29 mean (95% CI) trough forced expiratory volume in 1 s (FEV_1) (mL) of 215 (140,290) and 249 (170,320) respectively.

The aims of this study were to assess the pulmonary and systemic pharmacodynamics of single doses of inhaled GSK961081 alone and in combination with supratherapeutic doses of the short-acting bronchodilators salbutamol and ipratropium bromide, in patients with moderate to severe COPD. The effect of these treatments on the systemic pharmacokinetics of single doses of GSK961081 was also investigated.

2. Materials and methods

2.1. Study design and patient population

This was a multicentre, randomised, double-blind, complete crossover study. Eligible patients were male or female (non-child bearing) with moderate to severe COPD defined by a post-bronchodilator FEV_1 of between 40% and ≤80% of predicted normal and a post-bronchodilator FEV_1/forced vital capacity (FVC) ratio ≤0.7 [2]. Patients were aged 40–75 years with a body mass index of between 18 and 35 kg/m^2 and a minimum 10 pack year smoking history. All patients demonstrated reversibility to both salbutamol and ipratropium bromide, defined as an increase in FEV_1 of ≥12% and ≥150 mL following inhalation of each, at screening or documented within the previous 6 months. For patients with documented evidence an increase in FEV_1 of >6% and >100 mL at screening was also required. Percentage reversibility was calculated as (max FEV_1 post-bronchodilator) − (max FEV_1 pre-bronchodilator)/(max FEV_1 pre-bronchodilator) × 100.

Patients with poorly controlled COPD defined as use of antibiotics or an increased dose of ICS in the previous 6 weeks, more than two COPD exacerbations in the past 12 months, a respiratory tract infection in the previous 4 weeks, or clinically significant heart disease (defined as a history of congestive heart failure, coronary insufficiency or cardiac arrhythmia, or clinically abnormal electrocardiogram (ECG) or vital signs recordings) were excluded. Patients were not permitted treatment with inhaled cromolyn sodium, theophylline, oral β_2-agonists, nebulised anticholinergics or leukotriene antagonists; or treatment with LABAs and tiotropium from 72 h before screening or throughout the dosing period. Salbutamol was permitted as rescue medication during the study but was required to be withheld for 6 h before any lung function assessment. Treatment with ICS of <1000 μg fluticasone propionate (or equivalent) was permitted provided the dose was stable for 6 weeks before screening.

Patients were scheduled to receive the following 6 treatments with a washout of at least 7 days between treatments: Single doses of GSK961081 400 μg (MABA 400) or GSK961081 1200 μg (MABA 1200) followed by cumulative doses of either salbutamol (SALB) (3× 200 μg at 20 min intervals), ipratropium bromide (IPR) (20 μg, 20 μg and 40 μg at 20 min intervals) or placebo (PLA) (3 doses at 20 min intervals) at 1 h, 12 h and 24 h post-dosing. The MABA doses were administered via the Diskus (GlaxoSmithKline, London, UK); other treatments were administered via metered dose inhaler and spacer. MABA dose was blind to all patients and study staff. To maintain the study blind for SALB, IPR and PLA, treatments were administered to blindfolded patients by an unblinded study nurse, who did not participate in any safety or efficacy data interpretation or collect lung function assessments. The Principal Investigator and all other site staff were blinded to the study medications administered.

For each treatment period, treatment was administered in the investigator's unit on the morning of day 1 and patients were assessed and monitored over the following 27 h and were discharged on the morning of day 2. Patients fasted from midnight on day −1. They were given a standardised light breakfast in the morning that was consumed at least 2 h before any pre-dose procedures were performed. They then fasted until after the 4 h post-dose assessments had been completed.

The study protocol (study number MAB110123; NCT00674817) and informed consent were reviewed and approved by national and institutional ethics committees, as appropriate. Written informed consent was obtained from each subject prior to enrolment.

2.2. Study outcomes

2.2.1. Spirometry

The primary endpoint was the maximal increase in FEV_1, from pre-dose bronchodilator to post-bronchodilator (SABA/PLA) levels, measured 15 min after each cumulative dose of SALB, IPR or PLA at 1 h, 12 h and 24 h following a single dose of MABA 400 or MABA 1200. FEV_1 was also measured at 27 h after the MABA dose administration. The best of three technically acceptable measurements, made on an appropriately maintained and calibrated spirometer, was used.

2.2.2. Systemic pharmacodynamics

Heart rate (HR) and blood pressure (BP) were measured at baseline (pre-MABA dose) and at 2, 4, 9, 12, 13, 24 and 27 h post-MABA dose. HR was also measured 15 min after each dose of SALB, IPR or PLA; and blood pressure was also measured at 25 h post-MABA dose.

Full 12-lead ECG was measured at baseline and 2, 4, 9, 12, 13, 24, 25 and 27 h post-MABA dose. Patients were required to be withdrawn from the study if a QTc(B) or QTc(F) >500 ms or uncorrected QT >600 ms was recorded (or QTc(B) or QTc(F) >530 ms for patients with right bundle branch block).

Potassium and glucose monitoring was performed on whole blood samples using iSTAT portable chemical analysers, at baseline and 1, 2, 4, 12, 13, 24, 25 and 27 h post-MABA dosing. Any patients who had a sustained decrease in potassium below 3 mmol/L were required to be withdrawn from the study.

2.2.3. Adverse events and routine laboratory evaluations

Adverse events and serious adverse events were recorded throughout the study starting from day 1 of the first treatment.