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24-hour Bronchodilation following a single dose of the novel β_2-agonist olodaterol in COPD

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ABSTRACT

Background: Current guidelines recommend long-acting bronchodilators as maintenance therapy in COPD when symptoms are not adequately controlled with short-acting agents. Olodaterol is a novel long-acting β_2-adrenoceptor agonist with a pre-clinical profile that suggests 24-h bronchodilation may be achieved with once-daily administration.
Objective: To assess dose- and time-response in terms of bronchodilator efficacy, and to evaluate pharmacokinetics, safety and tolerability of single doses of olodaterol administered via Respimat® Soft Mist™ Inhaler in COPD patients.
Methods: A single-center, double-blind, placebo-controlled, 5-way crossover study including 24-h spirometry (FEV_1, FVC), safety, tolerability and pharmacokinetics (in a subset of patients) following dosing of olodaterol 2 μg, 5 μg, 10 μg and 20 μg; the washout period between test-days was at least 14 days. Primary endpoint of the study was the 24-h post-dosing FEV_1. Patients participating in the pharmacokinetic assessments continued in an open-label extension phase to establish pharmacokinetics of olodaterol 40 μg.
Results: 36 patients were assigned to treatment; mean baseline prebronchodilator FEV_1 was 1.01 L (37% predicted normal). All doses of olodaterol provided significantly greater bronchodilation compared to placebo in 24-h FEV_1 post-dose ($p < 0.001$); a clear dose–response relationship was observed, with values ranging from 0.070 L for olodaterol 2 μg to 0.119 L for olodaterol 20 μg. Similarly, olodaterol was superior to placebo ($p < 0.001$) in peak FEV_1 (0.121 L to 0.213 L) and average FEV_1 both during the daytime (0–12 h; ranging from 0.099 L to 0.184 L) and night-time (12–24 h; ranging from 0.074 L to 0.141 L). FVC results were consistent with those observed for FEV_1. Pharmacokinetic evaluation of the peak plasma concentrations and renal excretion suggested no obvious deviation from dose-proportionality over the investigated dose range of 2 μg–40 μg; in most patients, no plasma levels could be detected following the 2 μg dose. All treatments were well tolerated with no apparent dose relation in terms of adverse events.
Conclusions: Olodaterol appears to be a promising long-acting β_2-adrenoceptor agonist,with bronchodilation maintained over 24 h that offers an opportunity for once-daily dosing in patients who require maintenance bronchodilator therapy for the management of COPD symptoms.

1. Introduction

Inhaled long-acting bronchodilators play a central role in the symptomatic pharmacotherapy of patients with moderate to severe chronic obstructive pulmonary disease (COPD), a disorder characterized by a not fully reversible airflow limitation and a progressive deterioration in lung function over time. International guidelines recommend that these types of bronchodilator are introduced when symptoms persist with short-acting bronchodilators and maintenance therapy is required to prevent and control symptoms, and to improve the health status of patients [1,2].

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Currently, treatment options with inhaled long-acting bronchodilators include anticholinergics and β_2-adrenoceptor agonists. The anticholinergic tiotropium provides bronchodilation for more than 24 h [3,4], making it suitable for once-daily dosing, while β_2-adrenoceptor agonists salmeterol and formoterol show a duration of effect of 12 h and require twice-daily dosing [5–8]. Longer acting inhaled β_2-adrenoceptor agonists are under clinical development with the objective to prolong the duration of action and to achieve once-daily dosing [9,10]. The clinical benefits of these novel drugs would be bronchodilation over the whole 24-h dosing interval, an improved convenience for the patient and better compliance with therapy and, finally, the option for simplified combination therapy with other once-daily drugs like tiotropium.

Olodaterol belongs to this new generation of novel long-acting β_2-adrenoceptor agonists; the pre-clinical pharmacological profile of olodaterol has recently been described [11,12]. Olodaterol is a novel, enantiomeric pure, inhaled human β_2-adrenoceptor ($h\beta_2$-AR) agonist. *In vitro*, olodaterol showed a potent, nearly full agonistic response at the $h\beta_2$-AR (EC_{50} = 0.1 nM; intrinsic activity = 88% compared with isoprenaline) and a significant selectivity profile (219- and 1622-fold against the $h\beta_1$- and $h\beta_3$-ARs, respectively). *In vivo*, protective effects of single doses of olodaterol were measured against acetylcholine-induced bronchoconstriction in anesthetized guinea pigs and dogs for up to 24 h by using the Respimat SMI. In both models, olodaterol provided bronchoprotection over 24 h, suggesting that this novel β_2-AR agonist has the profile for once-daily dosing in humans.

In a recently completed study, inhaled olodaterol protected against methacholine-induced bronchoconstriction for up to 32 h following single dose administration in patients with intermittent asthma (range: 2–20 μg) [13]. All doses differed significantly from placebo and a dose-dependent effect was demonstrated. The objective of the present dose- and time-response study of olodaterol was to establish its 24-h bronchodilator efficacy and safety, and to characterize its pharmacokinetics following single dose administration in patients with COPD.

2. Methods

2.1. Patients

All patients were required to have a diagnosis of COPD [14], to be current or ex-smokers with a smoking history ≥10 pack-years and aged ≥40 years. Other eligibility requirements were: a baseline prebronchodilator $FEV_1 \leq 60\%$ predicted [15], an FEV_1/FVC ratio ≤70% at screening and at randomization (*i.e.* end of 2-week run-in period), and a bronchodilator responsiveness of at least 12% from baseline FEV_1 45 min after inhalation of 4 puffs of salbutamol 100 μg. Patients with asthma, allergic rhinitis, or a total blood eosinophil count ≥600/mm^3 were excluded. Additional specific exclusion criteria included a significant disease other than COPD, recent history of myocardial infarction, unstable or life-threatening cardiac arrhythmias, paroxysmal tachycardia, marked baseline prolongation of QTc interval (>450 ms) or history of additional risk factors for torsade des points [16], or therapy with oxygen, β-blockers, monoamine oxidase inhibitors or tricyclic antidepressants. No patients had experienced an exacerbation of COPD within the 8 weeks preceding randomization.

2.2. Study design

The trial was designed as a single-center, double-blind, placebo-controlled, 5-way crossover study (study code 1222.3; at the time the study was conducted there was no requirement to register explorative studies in the Clinical Trials Registry). Patients were randomly assigned to inhale a single dose of placebo or olodaterol (previously known as BI 1744) 2 μg, 5 μg, 10 μg or 20 μg delivered as an aqueous solution via Respimat® Soft Mist™ Inhaler (SMI; Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim am Rhein, Germany). The dose range chosen for the present study was based on considerations of the equipotency to formoterol in the aforementioned animal models: Foradil® MDI/Powder is regularly dosed at 9.8 μg with an assumed lung deposition of 20%, while Oxis® Turbuhaler is dosed at 4.9–9.8 μg with an estimated lung deposition of 30–40%. Following this, the deposited lung dose is ranging between 1.5 and 3.9 μg formoterol. Assuming a lung deposition of 40% with the Respimat® Inhaler, the effective nominal (nebulized) dose of olodaterol was estimated as 3.8–9.8 μg. With these calculations as a basis, a dose range from 2 μg to 20 μg was chosen for this initial study in COPD patients.

Following an initial screening visit to assess eligibility and a 2-week run-in period to ensure clinical stability, eligible patients completed 5 test-days, each consisting of a 24-h period of lung function testing, with each test-day separated by a washout period of at least 14 days. Following completion of the double-blind phase, those patients who agreed to participate in the pharmacokinetic sub-study were asked to continue in an open-label extension phase to evaluate pharamcokinetics following dosing of olodaterol 40 μg. Before screening and each 24-h test-day, patients were required to withdraw inhaled short-acting bronchodilators (8-h) and long-acting β_2-adrenergics (48-h washout). Oral β_2-adrenergics, tiotropium or theophyllines were not allowed for at least one month prior to and during the study period. Salbutamol MDI was provided to be used by the patients as rescue medication. Stable doses of inhaled steroids, oral steroids up to 10 mg/d of prednisone or mucolytics were allowed throughout the study. The medical ethics committee of the Atrium medisch centrum approved both study protocol and amendment (*i.e.* open-label pharmacokinetic extension), and written informed consent was obtained prior to any study-related procedure.

2.3. Assessments

2.3.1. Spirometry

Spirometry (FEV_1, FVC) was performed according to American Thoracic Society (ATS) criteria [17] using the Viasys Healthcare Masterscope. The highest values of FEV_1 and FVC from three technically adequate measurements were recorded. For initial screening of the patients qualifying tests were conducted before and 45 min after inhalation of salbutamol 400 μg; the post-salbutamol FEV_1 was measured to assess bronchodilator responsiveness (inclusion criterion) and to classify the patients' severity of their pulmonary impairment according to GOLD guidelines [1]. The test-days included serial spirometry over a 24-h period: 10 min before (between 07:00 and 10:00 a.m. with 30 min maximum difference between start at the randomization visit and subsequent 24-h pulmonary function test-days) and 30, 60 min, 2, 3, 4, 6, 8, 10, 14, 22, 23 and 24 h after single dose inhalation of study medication. If a patients' baseline FEV_1 at randomization was >1 L or ≤1 L, baseline FEV_1 at subsequent test-days had to be within 200 mL or 150 mL, respectively, of the baseline at randomization.

2.3.2. Additional observations

Additional observations on 24-h test-days included vital signs (just prior to each pulmonary function test), plasma potassium levels (sampling pre-dose and 20 min, 1, 2 and 4 h after study drug inhalation), 12-lead ECG monitoring (pre-dose and 10 min, 1, 2, 8 and 24 h post-dosing) and need for rescue medication (salbutamol MDI); adverse events and concomitant medication were monitored throughout the run-in period and randomized treatment period.