Relative systemic dose potency and tolerability of inhaled formoterol and salbutamol in healthy subjects and asthmatics

Received: 4 October 1999 / Accepted in revised form: 21 April 2000

Abstract Objectives: To compare the relative systemic dose potency and tolerability of inhaled formoterol and salbutamol and to describe elimination of formoterol, particularly any enantioselectivity.

Methods: Twelve healthy subjects, aged 18–28 years, completed three open study days, and eleven asthmatic patients, aged 20–56 years, completed four double-blind study days in randomised, placebo-controlled and crossover fashions. The healthy subjects inhaled 13.5 + 13.5 + 27 µg formoterol (Oxis) via Turbuhaler and 300 + 300 + 600 µg salbutamol (Ventoline) via a pressurised metered dose inhaler (pMDI). The asthmatics, being on formoterol 9 µg twice daily via Turbuhaler during the study, inhaled the same single doses as the healthy subjects plus 900 + 900 + 1800 µg salbutamol via pMDI. Doses were given cumulatively 30 min apart on separate study days. Placebo was a day of no treatment in the healthy subjects. Double blind were used for the asthmatics. Cardiovascular and metabolic effects were evaluated. Elimination of formoterol was addressed in the healthy subjects.

Results: Formoterol was estimated to be 28–109 times as potent as salbutamol, depending on the systemic effect

Introduction

Beta2-receptor agonists, such as salbutamol and formoterol, are used extensively as bronchodilators in the treatment of asthma. They are effective, but some systemic adverse reactions are seen after inhalation of high doses [1]. Two doses are available for administration of racemic formoterol fumarate dihydrate (hereafter “formoterol”, Oxis) via the dry powder inhaler Turbuhaler (4.5 µg and 9 µg per inhalation; in some markets denoted as metered doses of 6 µg and 12 µg per inhalation) and will be compared with the two doses of salbutamol normally available for administration via the pressurised metered dose inhaler (pMDI; 100 µg and 200 µg per inhalation). Formoterol is a long-acting bronchodilator after inhalation [2]. The maximum and 12-h average bronchodilating effect of formoterol 7 µg (delivered dose corresponding to 9 µg metered dose) inhaled via Turbuhaler is similar to that of salmeterol (Serevent) 50 µg inhaled via the dry powder inhaler Diskhaler [3].

Skeletal muscle tremor, palpitations, increased systolic and decreased diastolic blood pressure are well
known clinical side effects of β2-agonists. Cellular uptake of potassium [4] and glycogenolysis in the liver [5] are other systemic effects associated with β2-agonists. The consequence of hypokalaemia could be a prolonged Q-T interval [6]. Markedly reduced serum potassium concentration may be arrhythmogenic [7]. Because the supply of oxygen in the muscles and glycogenesis capacity are limited [5], plasma lactate might increase secondarily to the increase of plasma glucose.

The side effects of β2-agonists, e.g. the serum potassium suppression, are usually reduced during repeated treatment because extrapulmonary β2-adrenoreceptors are down-regulated [8, 9]. The tolerability and systemic side effects of formoterol inhaled via Turbuhaler have been studied in healthy subjects (data on file, AstraZeneca R&D Lund). Delivered doses up to 18 μg were well tolerated. Doses of 36 μg were considered clinically safe, although serum potassium was occasionally low and the incidence of tremor was higher than with lower doses. Tolerance was developed for these side effects during regular dosing.

It is recommended that multiple inhalations of a short-acting β2-agonist be used for rapid relief of bronchospasm in conjunction with acute asthma episodes [10]. As it has a rapid onset of action, it would be possible to use formoterol instead of the short-acting salbutamol in such situations.

To evaluate relative systemic dose potency of such therapy, with or without regular treatment with formoterol, magnitudes of selected cardiovascular and metabolic effects after cumulatively inhaled high doses of formoterol and salbutamol were compared in two separate studies, one in β2-agonist naive healthy subjects and one in asthmatic patients regularly treated with formoterol. Reported side effects and vital sign measurements were used to evaluate tolerability clinically. The elimination of formoterol, particularly any enantioselectivity, was described.

### Materials, methods and subjects studied

The two studies were performed in accordance with the Declaration of Helsinki and approved by the local ethics committees in Lund and Gothenburg. Before enrolment, healthy subjects and asthmatic patients gave informed consent after verbal and written information.

#### Definitions and symbols

- **Ae**: Amount of unchanged formoterol excreted in urine during a collection interval
- **Baseline**: Non-randomised study day in asthmatic patients after a 2-week β2-agonist washout
- **BPd**: Diastolic blood pressure
- **BPs**: Systolic blood pressure
- **F9**: Formoterol Turbuhaler 9 μg inhaled via Turbuhaler
- **F54**: Formoterol 13.5 + 13.5 + 27 μg inhaled via Turbuhaler
- **Glucose**: Plasma concentration of glucose
- **K+**: Serum concentration of the potassium ion, the primary variable
- **Lactate**: Plasma concentration of lactate
- **Placebo**: Randomised open study day in the healthy subjects or randomised double-blind study day in the asthmatic patients
- **Q-Tc (R:R)/(S,S)**: Heart-rate corrected Q-T interval
- **SI200, S3600**: Enantiomeric ratio of formoterol in urine
- **Salbutamol 300 + 300 + 600 μg and 900 + 900 + 1800 μg**, respectively, inhaled via pMDI
- **t1/2**: Apparent terminal half-life of formoterol

#### Healthy and asthmatic subjects

Eligibility was based on physical examination and standard clinical laboratory test results. Healthy subjects or asthmatic patients with a clinically relevant heart disease were not enrolled. Twelve healthy subjects were enrolled at the Phase I Unit, AstraZeneca R&D, Lund. All healthy subjects – six Caucasian men, one Oriental and five Caucasian women – of mean age 23 years (range 18–28 years) and mean weight 69 kg (range 58–82 kg) completed three study days. Thirteen asthmatic patients, diagnosed according to the American Thoracic Society criteria [11], were enrolled at one centre in Lund and one centre in Gothenburg. At enrolment, 12 patients inhaled budesonide regularly (200–1600 μg per day) and nine patients inhaled terbutaline when needed. Eleven patients, all Caucasian (six women) of mean age 34 years (range 29–56 years) and mean weight 76 kg (range 65–93 kg), completed five study days. Two asthmatic patients discontinued the study, and, as they did not complete the minimum of two study days, their results were included only in the description of data and not in the statistical analysis.

#### Protocol for healthy subjects

The healthy subjects completed three study days in an open, randomised, placebo-controlled and crossover fashion: 13.5 + 13.5 + 27 μg formoterol (Oxis) was inhaled via Turbuhaler and 300 + 300 + 600 μg salbutamol (Ventoline) was inhaled via pMDI. Placebo was a day of no treatment. It was assumed that 4.5 μg formoterol via Turbuhaler was equipotent with 100 μg salbutamol via pMDI. The three doses of formoterol and salbutamol were given cumulatively 30 min apart on separate occasions. In order to optimise drug delivery to the lungs and minimise intersubject variability, peak inhalation flows, measured using a Vitalograph MDI-Compact spirometer (Buckingham, England), had to be at least 60 l/min via Turbuhaler and 50 l/min at the most via pMDI. Before the second and third dose fractions, vital signs and spontaneously reported side effects were recorded. The washout between study days was at least 1 week.

During study days, controlled food intake was allowed only at 3 h, 6 h and 10 h after dosing was initiated. Strenuous activity and intake of beverages containing caffeine or alcohol were not allowed for at least 36 h before and during study days. Intake of other medicines was not allowed within 3 months before inclusion and during the study. Assessments were initiated after a 15-min rest, on the study days, before cumulative dosing was started or before a given reference time in the morning on the placebo day. Subsequent measurements were performed at 30 min after each dose (Q-Tc: only after the second dose increment) and after the last increment at predetermined times up to 3 h (plasma glucose and lactate), 6 h (plasma formoterol), 12 h (pulse, blood pressure, Q-Tc, and serum potassium) and 72 h (urinary excretion of formoterol).

#### Protocol for asthmatic patients

The asthmatic patients completed four study days in a double-blind, randomised, placebo-controlled and crossover fashion on top of formoterol (Oxis) 9 μg twice daily via Turbuhaler for at least 1 week. (The morning dose of the maintenance treatment was not taken on study days.) The following cumulative inhalations were...