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Salmeterol and fluticasone propionate given as a combination

Lack of systemic pharmacodynamic and pharmacokinetic interactions

Received: 23 March 2000 / Accepted in revised form: 13 October 2000 / Published online: 19 December 2000
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Abstract Objective: To investigate the potential for systemic pharmacodynamic and pharmacokinetic interactions between inhaled salmeterol and fluticasone propionate when repeat doses of the two drugs are given in combination to healthy subjects.

Methods: Twenty-eight healthy subjects received salmeterol 100 µg, salmeterol 100 µg/fluticasone propionate 500 µg and fluticasone propionate 500 µg via a Diskus dry powder inhaler twice daily for 11 days according to a randomised, double-blind, placebo-controlled, crossover design. Subjects in the placebo group also received a single dose of salmeterol 100 µg on the morning of day 10. On day 10, the systemic effects of salmeterol [on pulse rate, blood pressure, corrected QT (QTc) interval and serum potassium and glucose levels] and fluticasone propionate (on 24-h urinary cortisol and morning plasma cortisol levels) were assessed. Maximal number and affinity of lymphocyte β2-adrenoceptors and β2-adrenoceptor polymorphism at loci 16 and 27 were also determined. Plasma pharmacokinetics of salmeterol and fluticasone propionate were determined after the morning dose on day 10. Dosing continued on the evening of day 10 and on day 11, and on day 12 the effect of repeat-dose treatment with salmeterol and salmeterol/fluticasone propionate on the systemic effects of cumulative doses of inhaled salbutamol (up to a total dosage of 3200 µg) was evaluated.

Results: All treatments were safe and well tolerated. With the exception of a higher pulse rate after repeat administration of salmeterol [66.2 beats per minute (bpm) versus 63.6 bpm], there were no significant differences between the single-dose and repeat-dose salmeterol groups. The systemic pharmacodynamic effects of inhaled salmeterol were not affected by the co-administration of fluticasone propionate. Eleven days of treatment with salmeterol induced tachyphylaxis to the systemic effects of cumulative doses of salbutamol; however, co-administration of fluticasone propionate did not affect the response to salbutamol. Fluticasone propionate reduced 24-h urinary cortisol excretion (22.4 µg compared with 48.6 µg with placebo), but this was unaffected by the co-administration of salmeterol. Morning plasma cortisol levels were not reduced compared with placebo. There was no significant treatment effect on lymphocyte β2-adrenoceptors and no correlation of β2-adrenoceptor polymorphism at loci 16 and 27 with the development of tachyphylaxis. Salmeterol plasma concentrations were measurable only during the first half-hour after dosing. Co-administration of fluticasone propionate did not affect the peak plasma concentration (C_{max}) of salmeterol. For fluticasone propionate, there were no statistically significant differences between salmeterol/fluticasone propionate and fluticasone propionate with respect to C_{max} plasma concentration at the end of the dosing interval (C_t), terminal elimination half-life (t_{1/2}) or time to C_{max} (t_{max}). The area under the concentration–time curve within a dosing interval (AUC_t) for fluticasone propionate after inhalation of salmeterol/fluticasone propionate was statistically significantly higher (about 8%) than after inhalation of fluticasone propionate alone (P = 0.0135).
However, the 90% confidence intervals (CIs) for the
AUC\(_t\) and C\(_{\text{max}}\) ratios for the two treatments were
within the accepted limits for bioequivalence (1.03, 1.13 and
0.97, 1.12, respectively).

**Conclusion:** These results in healthy subjects indicate
that there is no systemic pharmacodynamic or phar-
macokinetic interaction between inhaled salmeterol and
fluticasone propionate when given in combination.

**Key words** Salmeterol · Fluticasone propionate · Combination

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**Introduction**

Asthma is a common, chronic inflammatory disease of
the airways characterised by wheezing, coughing and
tightness of the chest; prognosis of the disease is related
to the degree of airway obstruction and hyperrespon-
siveness [1]. Current treatment is based on the admin-
istration of \(\beta_2\)-adrenoceptor agonists to increase airway
calibre, which improves lung function and reduces the
incidence and severity of symptoms, and corticosteroids
to reduce inflammation, prevent asthma symptoms, de-
crease airway hyperresponsiveness and reduce the risk of
exacerbations [2]. To ensure effective treatment of both
inflammation and bronchoconstriction, corticosteroids
and bronchodilators are frequently administered
together. Current guidelines advocate the early intro-
duction of corticosteroids once a patient requires short-
acting bronchodilators more than once daily [3].

Fluticasone propionate is a topical corticosteroid that
has proven very effective in the treatment of asthma [4,
5, 6]. Its pharmacokinetic profile is characterised by high
pulmonary residence, rapid and extensive hepatic clear-
ance and negligible systemic bioavailability after oral
administration (<1%) [7, 8]. Salmeterol is a selective
long-acting \(\beta_2\)-agonist with dose-independent duration of
action [9, 10]. When given in combination with in-
haled corticosteroids, salmeterol produces a greater
improvement in lung function and symptom control [11,
12, 13] and significantly decreases the number of severe
exacerbations [14] compared with doubling the dose of
the corticosteroid.

Cytochrome \(P_{450}\) (CYP) 3A4 is involved in the me-
tabolism of both salmeterol [15] and fluticasone propi-
one [16], hence, there is a theoretical possibility of an
interaction when the two drugs are administered to-
gether. However, systemic exposure after inhalation of
either drug is very low, and as CYP3A4 is the most
abundant of all CYP \(P_{450}\) enzymes, its saturation by
salmeterol or fluticasone propionate is unlikely.

To provide optimal asthma therapy for patients who
remain symptomatic despite treatment with inhaled
corticosteroids and to aid compliance in patients re-
quiring regular treatment with both drugs, a combina-
tion of the long-acting \(\beta_2\)-agonist salmeterol and
fluticasone propionate has been developed in a dry
powder inhaler (Diskus inhaler). The combination is
available in three strengths, each containing salmeterol
50 \(\mu\)g, with fluticasone propionate either 100, 250 or
500 \(\mu\)g, which provide a range of doses to cover all
grades of asthma severity and are based on the dosage
recommendations for the individual component drugs.

The aim of this study was to investigate the potential
for systemic pharmacodynamic and pharmacokinetic
interactions between salmeterol and fluticasone propio-
ante when repeat doses of the two drugs are given in
combination to healthy subjects. This is the first study to
compare the systemic pharmacodynamic response to
and pharmacokinetics of repeat doses of a long-acting
inhaled \(\beta_2\)-agonist, an inhaled corticosteroid, their
combination and placebo in healthy subjects.

The development of \(\beta_2\)-adrenoceptor tachyphylaxis
to the systemic effects of salmeterol alone or in combi-
nation with fluticasone propionate was also assessed by
comparing the systemic pharmacodynamic response of
subjects given salmeterol and/or fluticasone propionate
to cumulative inhaled doses of the short-acting \(\beta_2\)-ag-
onist salbutamol. Lymphocyte \(\beta_2\)-adrenoceptors were
also measured to determine whether receptor down-
regulation had occurred.

The doses of salmeterol and fluticasone propionate
used in this study, 100 \(\mu\)g and 500 \(\mu\)g twice daily, re-
spectively, were chosen to be high enough to induce
measurable systemic effects in healthy subjects and to
maximise the potential for systemic pharmacodynamic
interactions between the two drugs, to allow reliable
measurement of drug plasma concentrations and not to
mimic clinical use. The drugs were administered for
11 days to ensure sufficient time for tachyphylaxis to the
pharmacodynamic effects of \(\beta_2\)-agonists to develop [17]
and for fluticasone propionate to reach steady state [18].
Salmeterol, even at doses much higher than the one
commonly used in clinical practice, produces peak
plasma concentrations that are maintained for only a
short period of time immediately after dosing (data on
file, study SLGB1004, GlaxoWellcome).

Recently it has been suggested that \(\beta_2\)-adrenoceptor
polymorphism at loci 16 and 27 may be associated with
susceptibility to develop tachyphylaxis to the effects of
\(\beta_2\)-agonist drugs [19, 20]. For this reason, the study
participants were genotyped retrospectively to investi-
gate whether a correlation existed in our population
between \(\beta_2\)-adrenoceptor genetic polymorphism and the
development of tachyphylaxis to the systemic pharma-
codynamic effects of repeat doses of salmeterol.

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**Materials and methods**

**Study design**

The study was of a randomised, double-blind, placebo-controlled,
3-period crossover design. Four treatments were compared:
salmeterol 100 \(\mu\)g, fluticasone propionate 500 \(\mu\)g, the combina-
tion of salmeterol 100 \(\mu\)g and fluticasone propionate 500 \(\mu\)g and pla-
cebo. Treatments were administered via a Diskus dry powder in-
haler twice daily for 11 days. Subjects randomised to the placebo