

- Barnes PJ. Effect of inhaled furosemide on metabisulfite and methacholine induced bronchoconstriction and nasal potential difference in asthmatic subjects. *Am Rev Respir Dis* 1990;142:576–80.
- 5 Seidenberg J, Dehning J, von der Hart H. Inhaled frusemide against cold air induced bronchoconstriction in asthmatic children. *Arch Dis Child* 1992;67:214–7.
- 6 Stevens EL, Vychara CFT, Southgate WM, Nakamura KT.

- Furosemide differently relaxes airway and vascular smooth muscle in fetal, newborn and adult guinea-pigs. *Am Rev Respir Dis* 1992;146:1192–7.
- 7 Silverman M, Anderson SD. Standardization of exercise tests in asthmatic children. *Arch Dis Child* 1972;47:882–9.
- 8 Pavord ID, Wisniewski A, Tattersfield AE. Inhaled frusemide and exercise induced asthma: evidence for a role of inhibitory prostanoids. *Thorax* 1992;47:797–800.

Thorax 1995;50:679–681

Salmeterol inhaler using a non-chlorinated propellant, HFA134a: systemic pharmacodynamic activity in healthy volunteers

S M Kirby, J Smith, G P Ventresca

Abstract

Background – Metered dose inhalers for the treatment of asthma use chlorofluorocarbons as propellants. These face an international ban due to their effect on the ozone layer. Salmeterol has been reformulated using the non-chlorinated propellant Glaxo inhalation grade HFA134a.

Methods – The safety, tolerability and systemic pharmacodynamic activity of the salmeterol/HFA134a inhaler, the current salmeterol inhaler, and placebo (HFA134a) were compared in 12 healthy volunteers in a double blind, randomised crossover study using a cumulative dosing design.

Results – Safety and tolerability were similar and the response was related to the dose over the range used (50–400 µg) with both salmeterol inhalers. The salmeterol/HFA134a inhaler showed no differences from the current inhaler for pulse rate, blood pressure, tremor, QT_c interval, and plasma glucose levels. The salmeterol/HFA134a inhaler had significantly less effect on plasma potassium levels.

Conclusions – In healthy volunteers the salmeterol/HFA134a inhaler is at least as safe and well tolerated as the current salmeterol inhaler, and has similar systemic pharmacodynamic activity.

(*Thorax* 1995;50:679–681)

Keywords: HFA134a, salmeterol, metered dose inhalers.

fluorocarbons as propellants which face an international ban on production from 1995–6 due to their depleting effect on the ozone layer. Because of their “essential use” status, temporary exemptions have been granted for the use of chlorofluorocarbons in metered dose inhalers while satisfactory alternatives are developed. Salmeterol has been reformulated in Glaxo inhalation grade HFA134a (tetrafluoroethane).

Studies in animals have shown HFA134a to be a non-toxic, inert compound. It was well tolerated when given alone to healthy subjects in single and repeat doses up to a maximum of 10 actuations four times daily for 14 days.² HFA134a is rapidly absorbed following inhalation, and rapidly eliminated from the body by ventilation, with no evidence of accumulation or significant metabolism.³

We have investigated the safety and tolerability of the salmeterol/HFA134a inhaler in healthy subjects and compared its systemic pharmacodynamic activity with that of the current salmeterol inhaler using chlorofluorocarbon propellant 11 and 12 (P11/P12).

Methods

Twelve healthy men of mean age 26.9 years (range 19–40) and mean weight 76.1 kg (range 59–92) gave their written informed consent. The study was approved by the local ethics committee and carried out in accordance with the provisions of the Declaration of Helsinki and later revisions.

Subjects received the salmeterol/HFA134a inhaler, the salmeterol/P11/12 inhaler, and placebo (HFA134a) in a double blind, randomised, three-way crossover manner on three different days at least one week apart. Salmeterol doses were cumulative: 50, 50, 100,

Clinical
Pharmacology
Division
S M Kirby
G P Ventresca

Department of
Medical Statistics
J Smith

Glaxo Research and
Development Ltd,
Greenford,
Middlesex UB6 0HE,
UK

Reprint requests to:
Dr G P Ventresca.

Received 9 September 1994
Returned to authors
9 November 1994
Revised version received
10 January 1995
Accepted for publication
6 February 1995

Salmeterol xinafoate is a potent, selective and long acting β_2 adrenoreceptor agonist used in the regular treatment of reversible airways obstruction¹ and available as a metered dose inhaler. Metered dose inhalers use chloro-

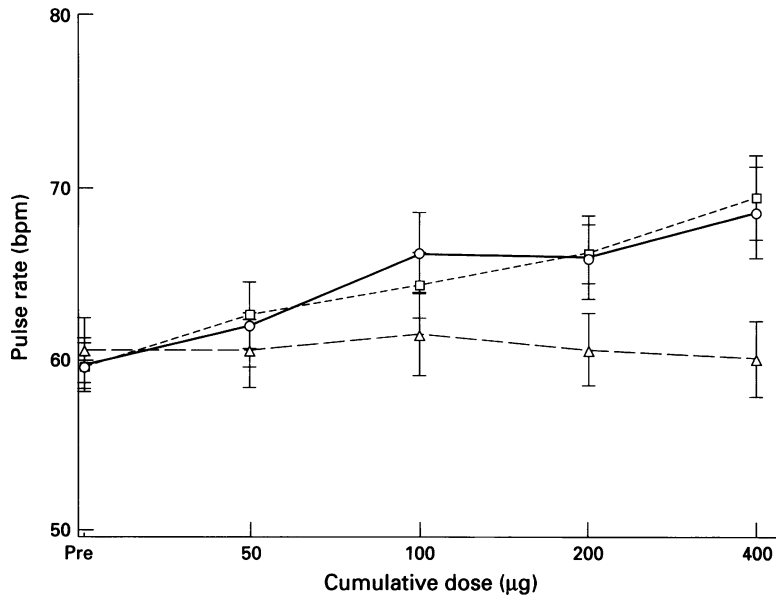


Figure 1 Mean (SE) pulse rate before and after cumulative doses of the salmeterol/HFA134a inhaler (○), the salmeterol/P11/12 inhaler (□), and placebo (△) in 12 subjects.

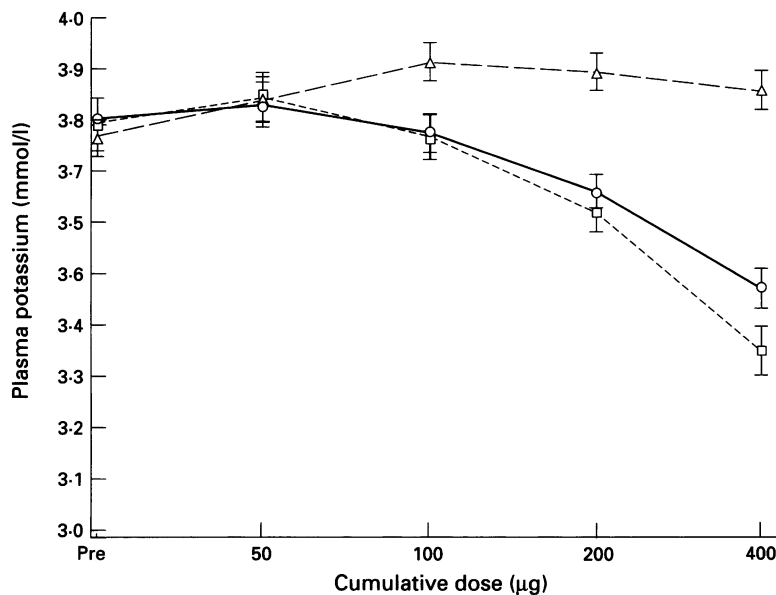


Figure 2 Mean (SE) plasma potassium levels before and after cumulative doses of the salmeterol/HFA134a inhaler (○), the salmeterol/P11/12 inhaler (□), and placebo (△) in 12 subjects.

and 200 µg at 60 minute intervals giving totals of 50, 100, 200, and 400 µg. The standard inhalation technique without a spacer was used.

The systemic pharmacodynamic response to salmeterol was determined by measuring pulse

rate and blood pressure, tremor, QT_c interval from a 12-lead ECG and rhythm strip, plasma levels of potassium and glucose, before dosing and at 30 and 55 minutes after each dose. Adverse events were recorded and special attention was paid to any cough and/or throat irritation at dosing. Routine laboratory safety screens were performed before and after the study and at the start of and 24 hours after each study day.

Each parameter was summarised by the final value after the last dose and the slope of linear regression of the dose-response curve (using means of values obtained at 30 and 55 minutes). Both were analysed using analysis of variance. The study had at least 90% power to confirm the equivalence of the two salmeterol treatments based on the 95% confidence intervals for the mean difference between them lying within ± 10 beats/min for pulse rate and ± 0.3 mmol/l for plasma potassium levels.

Results

The systemic pharmacodynamic response to the salmeterol/HFA134a inhaler was related to the dose over the dose range used; comparison of the salmeterol/HFA134a inhaler with placebo gave significant differences for the final values and the slope for all parameters measured (figs 1 and 2).

Comparison between the two salmeterol inhalers showed no significant differences, except for the final value of plasma levels of potassium (table) where the observed effects were less with the salmeterol/HFA134a inhaler. Analyses carried out using the maximum rather than the mean values gave similar results.

Eight adverse events (headache, cough and throat irritation), all of which were mild, were reported by five subjects. Cough at dosing occurred rarely and only with the last cumulative dose (eight actuations); twice with the salmeterol/HFA134a inhaler (once with throat irritation), and once with the current inhaler and placebo. There were no clinically significant changes in any of the laboratory parameters measured, or in the ECG traces.

Discussion

Inhaled medication is particularly valuable to patients with respiratory diseases because it delivers small quantities of drug directly to the lungs, thereby maximising efficacy and minimising side effects. Metered dose inhalers are

Mean (95% confidence interval) of systemic pharmacodynamic responses in 12 healthy subjects

Parameter	Salmeterol/HFA134a v placebo		Salmeterol/HFA134a v salmeterol/P11/12	
	Difference in final value	Difference in slope	Difference in final value	Difference in slope
Pulse rate (bpm)	8 (3 to 14)	1.9 (0.3 to 3.5)	-1 (-6 to 4)	-0.4 (-2.0 to 1.2)
Systolic BP (mm Hg)	8 (3 to 14)	2.6 (1.0 to 4.2)	0 (-5 to 6)	0.3 (-1.2 to 1.9)
Diastolic BP (mm Hg)	-8 (-13 to -3)	-1.5 (-2.5 to -0.6)	-1 (-6 to 4)	0.5 (-0.4 to 1.5)
Tremor* (units)	2.10 (1.67 to 2.65)	1.16 (1.08 to 1.24)	1.04 (0.83 to 1.30)	0.96 (0.90 to 1.03)
Plasma potassium (mmol/l)	-0.39 (-0.49 to -0.28)	-0.086 (-0.132 to -0.039)	0.12 (0.02 to 0.22)	0.042 (-0.004 to 0.088)
Plasma glucose (mmol/l)	0.90 (0.58 to 1.21)	0.177 (0.092 to 0.263)	-0.21 (-0.52 to 0.10)	-0.084 (-0.168 to 0.001)
QT _c (ms)	23 (8 to 33)**	-	2 (-6 to 12)**	-

*Ratio; **median.

the most common device for portable treatment and the pharmaceutical industry is committed to their reformulation without chlorofluorocarbons.

Salmeterol formulated with a chlorine-free hydrofluoroalkane, HFA134a, appeared to be at least as safe and well tolerated by healthy subjects as the current salmeterol inhaler, even at 4–8 times the standard therapeutic dose. Adverse events were rare and mild. There was very little cough or irritation at dosing, seen only with the highest number of actuations – a not unusual finding with metered dose inhalers, especially when many actuations are taken in rapid sequence. The administration of HFA134a did not appear to alter the safety and tolerability profile of salmeterol and there was no indication of any interaction; in particular, HFA134a did not appear to sensitise the cardiovascular system to the effects of salmeterol.

When administered in large doses inhaled β_2 adrenoreceptor agonists are associated with tremor and changes in cardiovascular, metabolic, and biochemical parameters. In healthy subjects these effects reach maximal levels one hour after administration of salmeterol.⁴ In this study the systemic pharmacodynamic response to salmeterol was investigated with sensitive

and clinically relevant parameters using a series of cumulative doses, spanning and exceeding the range in clinical use, to maximise the chances of revealing differences between formulations.

The only significant difference between the two salmeterol inhalers was observed on the final value of plasma levels of potassium which was smaller (0.12 mmol/l) than the pre-determined criterion of clinical significance (0.3 mmol/l). The observed effect was less with the salmeterol/HFA134a inhaler and is likely to be a chance finding. This small difference in one sensitive systemic parameter is unlikely to be reflected in any substantial change in the clinical profile of the drug.

- 1 Lötval J, Svedmyr N. Salmeterol: an inhaled β_2 -agonist with prolonged duration of action. *Lung* 1993;171:249–64.
- 2 Denyer LH, Kirby SM, Olsson P, Ventresca GP. HFA134a, a non-chlorinated propellant for use in metered-dose inhalers: safety, tolerability and blood pharmacokinetics in healthy volunteers. *Br J Clin Pharmacol* 1994;37:509–10P.
- 3 Olsson P, Aigbirhio FI, Freemantle CAJ, Pike VW, Page BC, Rhodes CG, *et al.* The absorption and disposition of a non-chlorinated propellant, GR106642X (1,1,1,2-tetrafluoroethane, HFA134a) as examined by ¹⁸F-labelling and whole-body counting in healthy subjects. *Am J Respir Crit Care Med* 1994;149:A220.
- 4 Maconochie JG, Forster JK. Dose-response study with high-dose inhaled salmeterol in healthy subjects. *Br J Clin Pharmacol* 1992;33:342–5.