

The therapeutic ratio of R-albuterol is comparable with that of RS-albuterol in asthmatic patients

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Background: It has been suggested that R-albuterol produces bronchodilation that is comparable with that of racemic albuterol (RS-albuterol) on a 4:1 dose-for-dose basis but systemic side effects on a 2:1 basis, implying better therapeutic ratio for R-albuterol.

Objective: We sought to carefully compare the bronchodilating and systemic effects of R- and RS-albuterol by using a crossover study design.

Methods: Twenty asthmatic patients (15.1%-28.7% FEV₁ reversibility) were given R-albuterol (6.25-1600 µg), S-albuterol (6.25-1600 µg), RS-albuterol (12.5-3200 µg), or placebo in a crossover, double-blind, placebo-controlled fashion. Cumulative doses were given with a Mefar dosimeter, and FEV₁, heart rate, and plasma K⁺ levels were measured 20 minutes after each dose.

Results: Both R- and RS-albuterol produced dose-related improvement in FEV₁ and, at higher doses, increased heart rate and decreased plasma K⁺ levels. Neither placebo nor S-albuterol had any significant effect. Individual estimates of the potency ratio for R-albuterol/RS-albuterol were calculated and summarized across all subjects. The geometric mean potency ratio for effects on FEV₁ was 1.9 (95% CI, 1.3-2.8), on HR of 1.9 (95% CI, 1.3-2.9), and on K⁺ level of 1.7 (95% CI, 1.3-2.1).

Conclusion: All pharmacologic effects of RS-albuterol reside with the R-enantiomer, and S-albuterol is clinically inactive. The R-albuterol/RS-albuterol potency ratios for local (FEV₁) and systemic effects (heart rate and K⁺) are similar, suggesting a comparable therapeutic ratio for R-albuterol and RS-albuterol in asthmatic subjects. (*J Allergy Clin Immunol* 2001;108:726-31.)

Key words: Asthma, bronchodilators, treatment, safety, β_2 -agonists

Albuterol is worldwide the most commonly used β_2 -agonist. In addition to their bronchodilating effects in the airways, all β_2 -agonists cause some systemic effects when given at high doses by means of the inhaled route, includ-

ing skeletal muscle tremor, palpitation, and increased heart rate, as well as reduced plasma potassium levels.¹

Albuterol contains an asymmetric carbon atom and hence is a chiral compound with R- and S-enantiomers.² Until recently, marketed albuterol preparations have been racemic (ie, 50:50) mixtures of the R(-)- and S(+)-enantiomers. It has historically been accepted that the β_2 -agonist activity of RS-albuterol resides solely with the R-enantiomer, with the S-enantiomer being pharmacologically inert. These conclusions are based on several in vitro β_2 -adrenoceptor binding and functional assays,³ whereas little is known of the in vivo effects in asthmatic individuals. Little attention has been paid to possible therapeutic advantages of the single enantiomer form of the compound.

The implication of the in vitro findings is that similar in vivo pharmacologic effects would be expected with a dose of R-albuterol half that of racemic RS-albuterol. This assumption has been confirmed in a healthy volunteer study comparing the systemic pharmacodynamic effects of nebulized R-, S-, and RS-albuterol.⁴ In these subjects R- and RS-albuterol were shown to be comparable on a 2:1 potency ratio, and the effects of S-albuterol were indistinguishable from those of placebo. However, 2 recent publications studying the effects of single and repeat nebulized doses of R- and RS-albuterol in adult⁵ and pediatric⁶ asthmatic patients have suggested that improved bronchodilation can be achieved with R-albuterol. In the adult study⁵ R-albuterol appeared to be 4-fold more potent than RS-albuterol (ie, 4:1 potency ratio), whereas in the pediatric study⁶ R-albuterol was apparently more than 4-fold more potent (ie, >4:1 potency ratio). Both studies indicated similar systemic effects when R- and RS-albuterol were compared on a 2:1 potency ratio, with the implication being that R-albuterol might have a better therapeutic index than RS-albuterol.

Our study was designed to compare the local bronchodilating and systemic pharmacodynamic effects of R- and RS-albuterol and the effects of S-albuterol and placebo. We chose to include asthmatic patients with reversibility of FEV₁ and gave a wide range of doses (6.25-3200 µg) administered by means of the inhaled route using a dosimeter technology. By doing this, we could determine, in a more exact manner, the therapeutic ratio of R- and RS-albuterol. The study also included pharmacokinetic sampling after each dose level to confirm that delivery of the single enantiomers was similar whether administered as the single enantiomeric form or as half of the racemate.

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Supported by a grant from Glaxo Wellcome Research & Development Limited.

Received for publication December 18, 2000; revised July 25, 2001; accepted for publication July 27, 2001.

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0091-6749/2001 \$35.00 + 0 1/81/119152

doi:10.1067/mai.2001.119152

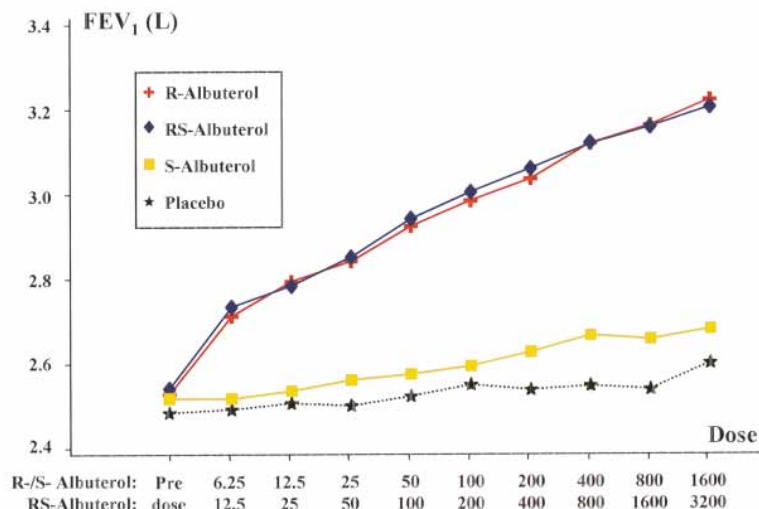


FIG 1. Mean effect of inhaled R-albuterol (6.25-1600 µg), S-albuterol (6.25-1600 µg), RS-albuterol (12.5-3200 µg), and placebo on FEV₁ in 20 patients with mild asthma.

METHODS

The study was approved by the Göteborg University Ethics Committee, and all patients gave their full written informed consent before entry into the study. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Trial Practice, and prior approval was obtained from the Swedish Medical Products Agency. The sponsor (GlaxoWellcome) monitored the study.

Patients and study design

Twenty patients (12 men; mean age, 50 years; age range, 24-70 years) with a documented history of asthma were recruited into the study. Inclusion criteria comprised a baseline FEV₁ of 60% or greater (mean FEV₁, 73% of predicted value; range, 60%-94%) and 15% or greater FEV₁ reversibility after 400 µg of nebulized RS-albuterol (mean FEV₁ reversibility, 19%; range, 15%-29%). Patients needed to be current nonsmokers who had not smoked for at least 12 months (7 nonsmokers and 13 exsmokers). Exclusion criteria included a lower respiratory tract infection within 4 weeks of entry, a history of life-threatening asthmatic attacks, and the presence of any other concomitant illness.

Within 1 week before the start of the randomized part of the study, patients underwent a screening visit in which compliance with the eligibility criteria was assessed and laboratory safety screens were conducted. Patients were not allowed to take any albuterol-containing products or long-acting β₂-agonists and were transferred onto terbutaline for use as rescue treatment from the time of screening and for the whole study period (to avoid interference with measurements of albuterol in the pharmacokinetic part of the study). Patients were allowed to continue to take their regular maintenance treatments (ie, inhaled corticosteroids and leukotriene modifiers) provided the regimen remained unchanged for the study duration.

After confirmation of eligibility, patients were entered into a placebo-controlled, randomized, double-blind, 4-way crossover study composed of 4 study days, each separated by a minimum 3-day washout period. Patients arrived at the clinic between 7 and 10 AM on each study day and were required to undergo a baseline FEV₁ test, which had to result in values no greater than 10% above or 20% below the baseline measurement determined at screening. Patients were randomized to receive R-albuterol, S-albuterol, RS-albuterol, or matching placebo, one per study day in a cumulative fashion. The

following doses were administered: 6.25, 12.5, 25, 50, 100, 200, 400, 800, and 1600 µg for S- or R-albuterol and 12.5, 25, 50, 100, 200, 400, 800, 1600, and 3200 µg for RS-albuterol. Doses were administered with a Mefar MB-3 dosimeter system at 25-minute intervals. Homochiral R- and S-albuterol sulfate (chiral purity, >99.9%) were prepared by Development Chemistry, Glaxo Wellcome R&D Limited (Stevenage, Hertfordshire, United Kingdom), by using a resolution process. The phenol and hydroxymethyl groups of racemic albuterol were protected as an isopropylidene acetal. Subsequent treatment of a hot solution of this material in ethyl acetate with (+)-(S,S)-ditolyltartaric acid furnished a thick precipitate, which was separated, basified, and hydrolyzed to give R-albuterol sulfate. The S-enantiomer was derived by treatment of the recovered scalemic isopropylidene acetal derivative with (-)-(R,R)-ditolyl-L-tartaric acid, basification, and hydrolysis. Nebulization solutions were supplied by Pharmaceutical Development, GlaxoWellcome R&D Limited (Ware, United Kingdom), in 5-mL glass vials containing 3 mL of RS-albuterol at 1.25, 10, and 20 mg/mL, or half the concentration of R- or S-albuterol in a phosphate-buffered formulation containing citric acid as a preservative.

Before dosing and 20 minutes after the administration of each dose, FEV₁ was measured with a Vitalograph Compact spirometer, and a 12-lead electrocardiogram was taken, from which heart rate (ventricular rate) was recorded. A 6-mL blood sample was also taken through a forearm vein cannula into a lithium heparin tube for measurements of plasma K⁺ levels, as well as R- and S-albuterol serum levels. Adverse event inquiries were also made after dosing and 20 minutes after each dose, and cardiac safety was monitored by using the electrocardiograms taken for pharmacodynamic measurements with any significant findings recorded as adverse events.

On completion of all study days, the patients returned to the clinic for poststudy safety screens (hematology, biochemistry, and urinalysis). These were compared with those taken at screening to determine whether there were any clinically significant changes that could be attributable to treatment.

Sample handling and bioanalysis

After collection, blood was immediately placed on ice and centrifuged at 1000g (4°C) for 10 minutes. Plasma was decanted into a 1-mL sample (for plasma K⁺) and a 1.5-mL sample (for plasma R- and S-albuterol), placed in storage vials, and stored at -20°C until analysis.

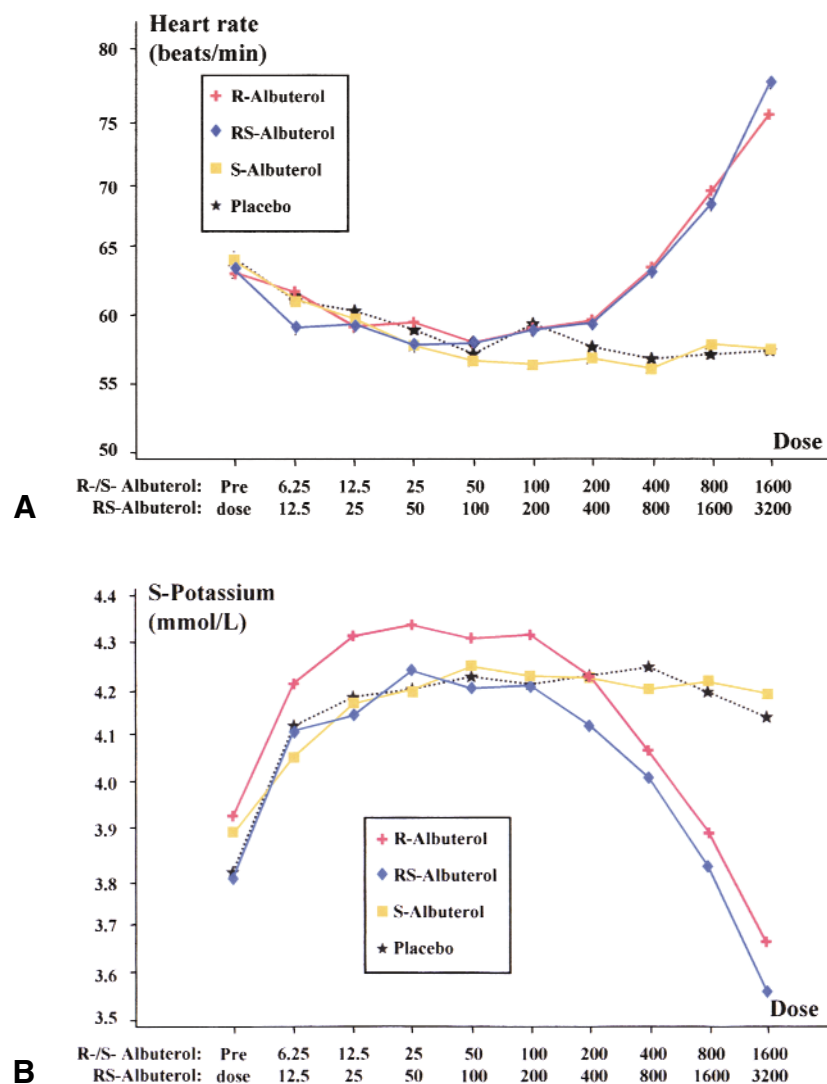


FIG 2. Mean effect of inhaled R-albuterol (6.25-1600 μ g), S-albuterol (6.25-1600 μ g), RS-albuterol (12.5-3200 μ g), and placebo on heart rate (A) and plasma K⁺ (B) in 20 patients with mild asthma.

The concentration of plasma K⁺ was determined with a Hitachi 917 auto-analyzer (Roche Diagnostics, Welwyn, United Kingdom) by using a neutral carrier-based liquid/liquid ion selective electrode. The lower limit of quantitation (coefficient of variation) was 1.5 mmol/L (1.2%). All analyses were carried out in the department of Clinical Pathology, Glaxo Wellcome Research & Development (Ware, United Kingdom), and the bioanalyst was blinded to the randomization code.

The plasma concentration of R- and S-albuterol enantiomers were determined by means of validated chiral methods involving solid-phase extraction, followed by chiral HPLC with tandem mass spectrometric detection by using a teicoplanin-based chiral stationary phase and selected reaction monitoring.⁷ The lower limit of quantitation (coefficient of variation) was 0.1 ng/mL (<7%). All analyses were carried out in the department of International Bioanalysis, Glaxo Wellcome Research & Development (Ware, United Kingdom), and the bioanalyst was blinded to the randomization code.

Data analysis

The statistical analysis was based on changes in FEV₁, plasma K⁺ levels, and heart rate. Individual potency ratios were calculated

from the data taken from individuals with linear dose-response relationships and parallel dose-response slopes for the active treatments (R- and RS-albuterol). The intercepts were adjusted for any differences at baseline. These data were then summarized across all subjects to obtain a population estimate of the geometric mean and 95% CIs. All statistical analyses were performed with SAS software (SAS version 6.12, SAS Institute, Cary, NC).

Plasma R- and S-albuterol levels measured at each time point were summarized across all subjects by using a median and represented graphically plotted against the preceding dose increment. Formal pharmacokinetic analyses were not appropriate because the drugs were administered with a cumulative-dose protocol. Instead, median profiles were used to investigate whether plasma exposure to each enantiomer was comparable whether the drugs were delivered as the single enantiomers or as part of the racemate.

RESULTS

Pharmacodynamics

Both R- and RS-albuterol (6.25-3600 μ g) produced significant and dose-dependent increases in FEV₁ (Fig

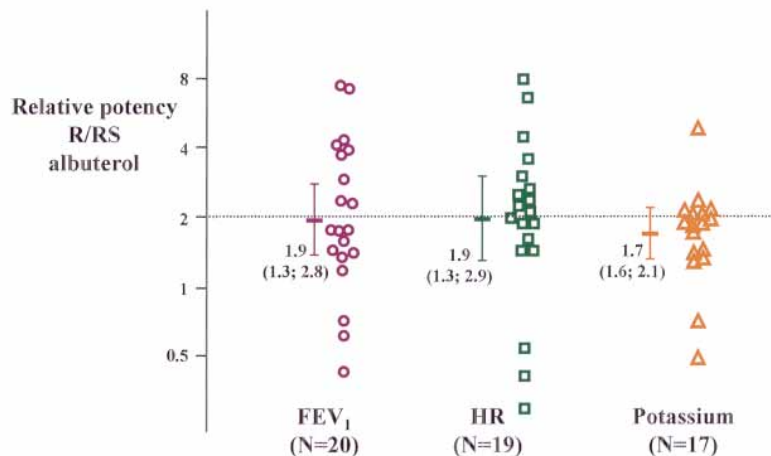


FIG 3. Mean (95% CI) and individual estimates of relative potency (R-albuterol/RS-albuterol) for FEV₁, heart rate, and plasma K⁺ level in patients with mild asthma.

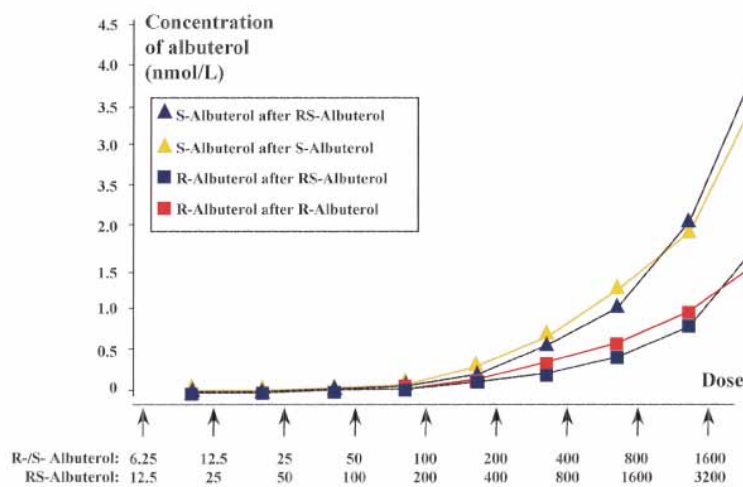


FIG 4. Median plasma concentrations of R- and S-albuterol after inhaled administration of single enantiomer R- or S-albuterol (6.25-1600 µg) or RS-albuterol (12.5-3200 µg) in 20 patients with mild asthma.

1). All doses significantly improved FEV₁ versus the effects of placebo. The dose-response curve did not consistently plateau at the higher doses of R- and RS-albuterol tested. At the highest doses of R- and RS-albuterol (ie, 1600 and 3200 µg, respectively), the maximum changes in FEV₁ from baseline were comparable (mean ± SE: 0.664 ± 0.08 and 0.686 ± 0.07 L/s, respectively). Compared with placebo, S-albuterol did not show any consistent effect on FEV₁ (Fig 1).

After placebo administration, and compared with pre-dose baseline values, there was a slight gradual decline in mean heart rate over the observation period (4-8 beats/min; Fig 2, A). There was also a rapid increase in plasma K⁺ level (0.3-0.4 mmol/L), which was consistently evident when predose samples were compared with those obtained immediately after the first dose of placebo. This initial increase in plasma K⁺ levels was maintained throughout the observation period. Compared with placebo, S-albuterol had no significant effect on heart rate or plasma K⁺ level at any dose tested. At doses of R-albuterol

of 200 µg or greater and doses of RS-albuterol of 400 µg or greater, dose-dependent increases in heart rate (Fig 2, A) and decreases in plasma K⁺ levels (Fig 2, B) were evident. At the highest doses of R- and RS-albuterol (1600 and 3200 µg, respectively), the maximum changes from baseline in heart rate and plasma K⁺ level were comparable (mean ± SE: 12.4 ± 3.0 beats/min, -0.26 ± 0.07 mmol/L and 14.0 ± 2.9 beats/min, -0.24 ± 0.07 mmol/L, respectively). At similarly high doses, both R- and RS-albuterol produced dose-related increases in the QTc interval (data not shown), up to a maximum of 0.05 seconds. The inherently high variability of this measurement made it difficult to identify clear dose-response relationships.

In 1 subject for heart rate and 3 subjects for plasma K⁺ level, there was no evidence of a clear dose-response relationship for either R- or RS-albuterol, and data from these individuals were therefore not used in the analysis. Mean potency ratios were 1.9 (95% CI, 1.3-2.8), 1.9 (95% CI, 1.3-2.9), and 1.7 (95% CI, 1.3-2.1) for FEV₁, heart rate, and plasma K⁺ level, respectively (Fig 3). There was no

TABLE I. Listing of adverse events experienced by 20 asthmatic patients receiving R-albuterol (6.25-1600 µg), S-albuterol (6.25-1600 µg), RS-albuterol (12.5-3200 µg), or matching placebo

Adverse event	RS-albuterol	R-albuterol	S-albuterol	Placebo
All events				
No. of subjects reporting adverse events	14	13	6	7
Total No. of adverse events	30	24	8	10
β ₂ -Mediated events				
Total	20	17	1	0
Tremor	9	7	1	0
Palpitations	7	8	0	0
Tachyarrhythmias	3	2	0	0
Agitation	1	0	0	0
Other events				
Total	10	7	7	10

correlation between potency ratios for FEV₁ and heart rate or plasma K⁺ level or between those measured for heart rate and plasma K⁺ level measured within the same subject (data not shown). This suggested that the difference between these ratios is randomly distributed and likely to be due to inherent variability, rather than reflecting differing local or systemic delivery of R- and RS-albuterol.

Safety

There were no serious adverse events and no withdrawals from the study because of drug-related adverse events (Table I). There were also no clinically significant changes in laboratory parameters when poststudy samples were compared with prestudy samples. The majority (54/72) of adverse events were reported after treatment with R- or RS-albuterol, with the events reported after S-albuterol being comparable with those after placebo in both nature and frequency. The nature, frequency, and severity of adverse events after treatment with R- or RS-albuterol were comparable.

Pharmacokinetics

Median plasma concentrations of R- and S-albuterol measured after inhalation of both of the single enantiomeric forms or the racemate are shown in Fig 4. After administration of R-albuterol, S-albuterol was not reproducibly detected in plasma and vice versa. However, both R- and S-albuterol were detectable in plasma after administration of RS-albuterol, with S-albuterol levels exceeding those of R-albuterol, especially after the higher doses of the treatments. Levels of R- or S-albuterol were comparable whether administered as their single enantiomers or as half of the racemic mixture (median [R-albuterol]_{plasma}: after 100 µg of R-albuterol = 0.156 ng/mL; after 200 µg of RS-albuterol = 0.170 ng/mL; median [S-albuterol]_{plasma}: after 800 µg of S-albuterol = 1.83 ng/mL; after 1600 µg of RS-albuterol = 1.96 ng/mL).

DISCUSSION

This study, using a more than two-¹⁰log cumulative dose-response design, shows that R- and RS-albuterol have a 2:1 potency ratio for improvement in FEV₁ in asthmatic patients and shows that S-albuterol is clinical-

ly inactive. Because the RS-albuterol mixture contains only 50% R-albuterol, it is clear that the clinical effect of albuterol resides with the R-enantiomer. Furthermore, the therapeutic ratios of R- and RS-albuterol are very similar, suggesting that the S-enantiomer of albuterol does not affect its therapeutic ratio.

Thus half of the dose of R-albuterol compared with RS-albuterol was required to reach similar bronchodilation, as well as similar systemic side effects on heart rate and plasma K⁺ level. This further supports the argument that the S-component of racemic albuterol is inert and that in patients all pharmacologic activity resides with the R-enantiomer. Compared with placebo, S-albuterol was shown to be inactive as a bronchodilator, confirming the results of previous studies that have evaluated the effect of the enantiomers on isolated human airway smooth muscle in vitro. Importantly, in our study the FEV₁ values after 1600 µg of S-albuterol are less than the ones observed after 6.25 µg of R-salbutamol, suggesting that any contamination with R-albuterol (or any β-mediated activity of the inhaled S-albuterol solution) is numerically very small.

The inactivity of S-albuterol is further documented by the lack of systemic effects of this treatment (Figs 2 and 3). Thus this study further supports the conclusion that S-albuterol is inert in human subjects in vivo. The conclusions from some studies, suggesting that the S-component could add to side effects and be detrimental for the treatment of asthma,⁸ may therefore not be correct. Importantly, these studies have generally been of parallel-group design with low numbers of subjects, and large variability may therefore have affected the data.

By using a very wide dose range in this study, we could prove that bronchodilation to albuterol is indeed dose related. However, in this selected patient population, approximately 60% of the dose dependency is present at doses lower than those clinically available (100 µg). This supports the concept that the doses of albuterol used in clinical practice are high on the dose-response curve. However, the dosimeter system we used to administer albuterol may be of higher efficiency than a pressurized metered-dose inhaler or dry powder inhaler.⁹

Pharmacokinetically, it is well known that S-albuterol reaches higher circulating concentrations than R-

albuterol after inhalation of the racemate. This is believed to be due to presystemic stereoselective metabolism of R-albuterol, which occurs in the gut and systemic circulation,¹⁰ but not in the lungs.¹¹ This is confirmed in the present study, in which we observed higher levels of circulating S-albuterol than of R-albuterol after higher doses of drug (Fig 4), which is likely to reflect gastrointestinal absorption of high doses of inhaled drug.

The concentrations of the R- and S-isomers of albuterol were similar, regardless of whether the compounds had been given as single isomers or as racemate. It has also been suggested that S-albuterol could affect the pharmacokinetics of R-albuterol,¹⁰ but in this study the concentrations of the R-isomer were similar, regardless of whether this isomer was given alone or together with the S-form in the racemate. This finding also suggests that there is no interconversion of S-albuterol to the R-form or vice versa.

The wide dose range used in this study also allowed us to calculate the therapeutic ratio of albuterol in these asthmatic patients. On average, 50% of the bronchodilation induced by albuterol is present at approximately 70 µg of RS-albuterol/35 µg of R-albuterol (Fig 1). Approximately 4 additional doubling doses are required to detect increases in heart rate or reduction in plasma K⁺ levels (Fig 2). The heart rate change is, however, only 5 beats/min at this level, and even higher doses are required to cause systemic effects that are likely to cause subjective symptoms. Importantly, no differences in systemic effects or in potency ratios were observed between the R-enantiomer and the racemate.

In summary, this study shows that the bronchodilation and systemic effects of albuterol reside with the R-enantiomer and that the S-enantiomer is inert, contrary to what has been argued.¹² Thus the safety of the commonly used albuterol racemate is similar to that of the single R-enantiomer, as was recently suggested.¹³

We thank Drs Karina Joyce and Stephen Pleasance (International Bioanalysis) and Dr Malcolm York (Clinical Pathology), Glaxo-

Wellcome R&D Ltd, Ware, United Kingdom) for their bioanalytic support. We also thank Helen Törnqvist, Eva Karlgren, and Marianne Robertsson of the Lung Pharmacology Group, Göteborg University, Sweden, for their help with the clinical phase of the study.

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