

Salbutamol inhibits metabisulphite-induced bronchoconstriction

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The effect of salbutamol on bronchoconstriction induced by inhaled sodium metabisulphite has been studied in 12 atopic subjects. Salbutamol (200 µg, 3.5×10^{-7} M) and matched placebo were administered by identical metered dose inhaler 15 min before a dose-response to sodium metabisulphite (1.25–100 mg ml⁻¹) was performed. Geometric mean provocative dose of metabisulphite causing a 35% fall in sGaw after placebo pre-treatment was 12.8 [5.75–28.1, 95% CI] µmol, and after salbutamol was 75.9 [46.5–126] µmol. Mean maximum fall in sGaw after placebo pre-treatment was 47.4 [41–53.9] %. At the same metabisulphite concentration mean maximum fall in sGaw after salbutamol was 2.9 [–8.2–14.1] %.

Keywords salbutamol sodium metabisulphite bronchoconstriction

Introduction

Sodium metabisulphite (MBS) is one of the most widely used preservatives in the food and pharmaceutical industry. Inhalation of increasing concentrations of MBS has been shown to be a safe and reproducible laboratory method of inducing bronchoconstriction in asthmatic and atopic subjects (Dixon & Ind, 1990; Nichol *et al.*, 1989).

Bronchoconstriction induced by MBS can be prevented by prior inhalation of nedocromil, and inhibited to a lesser extent by cromoglycate (Dixon & Ind, 1990), frusemide (Nichol *et al.*, 1990), and least of all by atropine-like drugs (Dixon & Ind, 1988; Nichol *et al.*, 1989).

Salbutamol is a specific β_2 -adrenoceptor agonist which has been shown to prevent SO₂ induced bronchoconstriction in adolescents (Koenig *et al.*, 1987), but its effect on MBS induced bronchoconstriction has not been formally studied. The aim of this study was to examine the effect of inhaled salbutamol pretreatment on MBS induced bronchoconstriction.

Methods

Twelve atopic subjects were studied six of whom had mild asthma. All gave written informed consent to the study, which had the approval of the hospital Ethics Committee. Atopic status was determined by positive skin weal and flare reactions to five common antigens. Asthmatic subjects used only inhaled β_2 -adrenoceptor agonists when necessary.

Subjects were studied in a double-blind randomised manner on 2 days within the space of 1 week. On each occasion specific airways conductance (sGaw) was determined, as the mean of six readings, by computerised body plethysmography (Chowienzyk *et al.*, 1981). Subjects then received at random either salbutamol 200 µg or matched placebo by metered dose inhaler. SGaw was repeated 15 min later. Five inhalations of normal saline were then administered by a breath actuated dosimeter (Mefar, Brescia, Italy), driven by compressed air at 15 psi with a 1 s actuation time, delivering 0.024 ml of solution per inhalation. SGaw was measured 90 s after saline inhalation. Metabisulphite challenge was performed if post-saline sGaw was within 10% of baseline.

Sodium metabisulphite (Sigma, Poole, Dorset) was freshly dissolved in 0.9% normal saline to give solutions with concentrations of 1.25, 2.5, 5, 10, 25, 50 and 100 mg ml⁻¹. Increasing concentrations were inhaled at 3 min intervals. SGaw was repeated 90 s after each inhalation. Challenge was terminated after a fall in sGaw of greater than 35% of after the highest concentration of metabisulphite. Log dose-response curves were constructed and PD₃₅, that is the cumulative provocative dose of metabisulphite causing a 35% fall in sGaw, determined by linear interpolation.

Baseline sGaw values and log-transformed PD₃₅ values were analysed by multifactorial analysis of variance (ANOVA). The effect of drugs on baseline sGaw was analysed by ANOVA for repeated measures. Where a fall in sGaw of 35% was not achieved after the highest concentration of MBS a censored value of 120 µM was assigned.

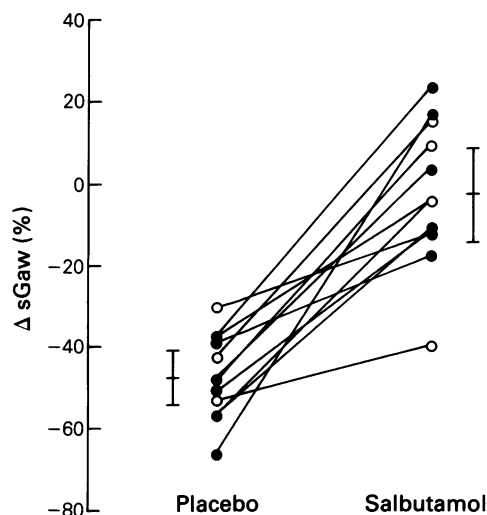


Figure 1 Individual values of change in sGaw after placebo and salbutamol pretreatment achieved at the highest concentration MBS inhaled on placebo day. Asthmatic atopic subjects are shown as closed circles (●). Non-asthmatic atopic subjects are shown as open circles (○). Bars represent mean and 95% confidence interval.

Results

Mean baseline sGaw was 1.83 [1.57–2.01, 95% CI] $\text{kpa}^{-1} \text{s}^{-1}$ before placebo and 1.77 [1.45–2.09] $\text{kpa}^{-1} \text{s}^{-1}$ before salbutamol ($P = 0.7$). sGaw was 2.28 [1.85–2.71] $\text{kpa}^{-1} \text{s}^{-1}$ 15 min after salbutamol compared with 1.89 [1.52–2.26] $\text{kpa}^{-1} \text{s}^{-1}$ 15 min after placebo ($P < 0.005$).

Geometric mean PD_{35} , calculated from the pre-drug baseline, was 12.3 [5.3–29.0, 95% CI] μmol on placebo day compared with 101 [77–131] μmol on salbutamol day ($P < 0.001$). Geometric mean PD_{35} , calculated from the 15 min post-drug baseline, was 12.8 [5.75–28.1] μmol on placebo day compared with 75.9 [46.5–126] μmol on salbutamol day ($P < 0.001$). After salbutamol eight subjects (four asthmatics) failed to achieve a 35% fall in sGaw after MBS challenge. We therefore compared the % fall in sGaw at the highest concentration of MBS inhaled on placebo day. Mean reduction in sGaw was

47.4 [41–53.9] % after placebo compared with 2.94 [–8.2–14.1] % after salbutamol at the same concentration of MBS ($P < 0.001$, Figure 1). All subjects showed protection from salbutamol. Baseline sGaw, change after salbutamol and degree of protection against MBS did not differ significantly between asthmatic and non-asthmatic subjects.

Discussion

Significant protection against MBS-induced bronchoconstriction was demonstrated by a mean 16.9-fold increase in PD_{35} after salbutamol 200 μg , and complete protection when comparing response at the highest MBS concentration achieved on placebo day. A similar degree of protection has been reported for 180 μg salbutamol against SO_2 -induced bronchoconstriction (Koenig *et al.*, 1987). β_2 -adrenoceptor agonist drugs protect against induced bronchoconstriction whatever the stimulus – so called physiological antagonism. MBS-induced bronchoconstriction is no exception.

Comparison of the effect of salbutamol with the effect of other agents on MBS-induced bronchoconstriction is difficult due to the censoring of data in this study. However, salbutamol appears to offer greater protection than anticholinergic agents (Dixon & Ind, 1988; Nichol *et al.*, 1989), sodium cromoglycate (Dixon & Ind, 1990), or frusemide (Nichol *et al.*, 1990). Nedocromil also produced complete inhibition of the response to MBS (Dixon & Ind, 1990).

The rapid speed of onset of MBS-induced bronchoconstriction (Nichol *et al.*, 1989) together with the significant protection afforded by salbutamol suggest that MBS induces airway narrowing mainly via bronchial smooth muscle constriction rather than by laryngeal effects, oedema formation or airway inflammation.

In conclusion, we have demonstrated that salbutamol 200 μg significantly protects against MBS-induced bronchoconstriction. This suggests that smooth muscle constriction is mainly responsible for the airway narrowing, but the underlying effector pathway is still uncertain.

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