Eur Respir J, 1994, 7, 2160–2164
DOI: 10.1183/09031936.94.07122160

European Respiratory Journal
ISSN 0903 - 1936

Incidence of acute decreases in peak expiratory flow following the use of metered-dose inhalers in asthmatic patients

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Incidence of acute decreases in peak expiratory flow following the use of metered-dose inhalers in asthmatic patients. M.Z. Shaheen, J.G. Ayres, C. Benincasa. ©ERS Journals Ltd 1994.

ABSTRACT: This study aimed to investigate and compare the incidence of metered-dose inhaler (MDI)-associated bronchoconstriction in an asthmatic population, following the use of three different MDIs. Two different placebo metered-dose inhaler preparations containing the same chlorofluorocarbons but differing in dispersant chemicals, one containing oleic acid (MDI-OA) and the other lecithin NF (MDI-L), were compared with a MDI containing salmeterol xinafoate (25 µg) and lecithin NF (MDI-S).

The study population comprised 11,850 asthmatic patients, who were assigned to receive two puffs from one of the three inhalers: MDI-S (n=3,948); MDI-L (n=3,942); or MDI-OA (n=3,960). Peak expiratory flow (PEF) was measured before and 5 min after inhalation. A 20% fall in PEF was defined as a clinically significant bronchoconstriction.

Overall 180 (1.5%) patients demonstrated bronchoconstriction, 43 (1.1%) in the MDI-S group, 67 (1.7%) in the MDI-L group and 70 (1.8%) in the MDI-OA. A significantly lower incidence of bronchoconstriction was seen with the salmeterol xinafoate MDI compared to either of the other two preparations. The risk of acute bronchoconstriction was also shown to increase with age and with decreasing pre-treatment PEF.

The study has shown that acute bronchoconstriction is an uncommon adverse reaction following the use of metered-dose inhalers. In addition, the study suggests that one of the inert constituents currently within metered-dose inhalers is the likely source of the irritant leading to bronchoconstriction.

Eur Respir J., 1994, 7, 2160–2164.

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Keywords: Acute bronchoconstriction
chlorofluorocarbons
lecithin NF
metered-dose inhaler
oleic acid
salmeterol xinafoate

Received: February 11 1994
Accepted after revision August 23 1994

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Bronchoconstriction associated with the inhalation of drugs is a relatively uncommon event, but one that is known to occur with all therapeutic agents given by inhalation [1–4].

Bronchoconstriction associated with the use of inhaled bronchodilator drugs has been of particular interest because of its apparent paradoxical nature compared to the anticipated pharmacological effects [5]. Reports in the literature have been infrequent [6, 7]. The metered-dose inhaler (MDI) being the most commonly used device for the delivery of drugs *via* the inhaled route has, however, been the subject of the majority of these reports [8, 9]. The basis for this bronchoconstriction is at present poorly understood, although the osmolarity [10], acidity [11], individual inert constituents that make up the aerosol preparation [12, 13], and the deep inspiration required for inhalation of the drugs [14], have all been suggested as possible causative factors.

Salmeterol xinafoate, a new selective, long-acting, inhaled bronchodilator has recently been introduced for the treatment of asthma [15, 16]. Since the time of its availability, there have been reports of bronchoconstriction associated with the use of salmeterol xinafoate MDI [17]. A study of six patients known to have acute bronchoconstriction in response to salmeterol xinafoate MDI suggested that one of the "inert" constituents within the MDI may have been responsible for the bronchoconstriction [18].

Since the salmeterol xinafoate MDI had a different dispersant chemical to many other available MDIs, it seemed important to compare the two different dispersant chemicals. Therefore, this study was designed to investigate the incidence of bronchoconstriction associated with salmeterol xinafoate MDI, and to compare this incidence with that found with two placebo MDI preparations containing chlorofluorocarbons (CFCs) and different dispersant chemicals, in a population of nearly 12,000 adult asthmatics.

Patients and methods

The study was of a multicentre, double-blind, single dose, randomized, parallel group design involving 519 UK centres and 11,850 patients, recruited between October 1991 and February 1992.

Adult asthmatic patients aged 18 yrs or more who, in the investigator's opinion, were able to use an MDI correctly and who had not previously taken salmeterol xinafoate, were eligible for the study. Patients continued on their usual asthma therapy: however, they were excluded if they were currently receiving a short course of oral corticosteroid or had suffered from an exacerbation of asthma within 2 weeks prior to the study. In addition, they were not to have had inhaled $beta_2$-adrenoceptor agonist for 4 h prior to the study, or oral $beta_2$-adrenoceptor agonists, xanthines or inhaled oxitropium bromide in the 8 h prior to the study. Patients were randomized to receive two puffs from one of the following metered-dose inhalers: 1) MDI-S - containing salmeterol xinafoate (25 μg·puff^{-1}), lecithin dispersant, trichloromonofluoromethane and dichlorodifluoromethane; 2) MDI-L - placebo inhaler containing lecithin dispersant, trichloromonofluoromethane, and dichlorodifluoromethane; or 3) MDI-OA - placebo inhaler containing oleic acid dispersant, trichloromonofluoromethane, and dichlorodifluoromethane.

The contents of MDI-S were identical to those found in commercial supplies of salmeterol xinafoate MDI, whilst MDI-OA contained the same dispersant and propellant chemicals found in commercial supplies of salbutamol.

Peak expiratory flow (PEF) was measured using a mini-Wright peak flow meter (best of three blows), before and 5 min after inhalation of two puffs from one of the treatments. Inhaled salbutamol (in dry powder form) was given to any patient who experienced symptoms of bronchoconstriction following inhalation from one of the study MDIs.

The study was granted ethical approval from the relevant Ethics Committees and written informed consent was obtained from each patient before their participation in the study. The study was conducted in accordance with good clinical practice with a team of 17 research personnel monitoring centres on a 3 weekly basis.

It was estimated that in order to detect a difference in incidence of 1% between treatments with 90% power, 3,098 patients per group would be required. For the purpose of this study, clinically relevant bronchoconstriction was defined as a 20% or more decrease in PEF compared to pretreatment, measured 5 min after inhalation from MDI-S, MDI-L or MDI-OA. The incidence of bronchoconstriction was compared between the three groups using the normal approximation to the binomial test. Estimates of treatment differences were calculated together with the 95% confidence intervals. In addition, a multiple logistic regression analysis was performed fitting treatment group, age category and pretreatment PEF as additive factors and covariates in the model. The patients' pretreatment PEF's were categorized into the following groups; 1) patients with a PEF greater than 100% of their predicted normal value; 2) patients with PEF greater than 50% and up to 100% of their predicted normal value; and 3) patients with a PEF of 50% or less of their predicted normal values. The analysis also investigated the presence of an interaction effect between age category and pretreatment PEF. The multiple logistic regression analysis was carried out using the GLIM system Release 3.77, whilst the remainder of the analysis was carried out using SAS PC version 6.04.

Results

Of a total of 11,850 patients entered into the study, 3,948 received MDI-S, 3,942 MDI-L and 3,960 MDI-OA. All three groups were comparable with respect to their demographic details (table 1). Although the minimum age criterion was 18 yrs, there were 20 patients in the MDI-S group, 32 in the MDI-L group, and 13 in the MDI-OA group who were aged less than 18 yrs. These patients were included in the analysis.

Overall, a total of 180 (1.5%) of the patients had a decrease of 20% or greater in PEF following MDI inhalation. This included 43 (1.1%) for MDI-S, 67 (1.7%) for MDI-L, and 70 (1.8%) for MDI-OA. There was a statistically significantly lower incidence of bronchoconstriction with MDI-S compared with either MDI-L (p=0.021; 95% confidence interval (95% CI)=-1.1%

Table 1. – Demographic details of the total sample population for the three groups MDI-S, MDI-L and MDI-OA

		MDI-S n=3948	MDI-L n=3942	MDI-OA n=3960
Sex %	Female/Male	54/46	53/47	53/47
Age yrs*		48±18	47±18	48±18
		(11–89)	(8–89)	(13–90)
Age catergories n†	<18 yrs	20	32	13
	18–20 yrs	157	147	128
	21–40 yrs	1,315	1,375	1,368
	41–60 yrs	1,206	1,194	1,179
	61–80 yrs	1,181	1,122	1,189
	>80 yrs	67	69	80
Height cm*		167±10	167±10	167±10
		(122–198)	(136–208)	(122–199)
Baseline PEF $l \cdot min^{-1}$**		380±130	384±131	381±130

*: data are presented as mean±SD, and range in parenthesis; **: data are presented as mean±SD. †: some ages not known (2 MDI-S, 3 MDI-L, 3 MDI-OA). PEF: peak expiratory flow; MDI: metered-dose inhaler; MDI-S: MDI containing salmeterol xinafoate (25 μg) and lecithin NF; MDI-L: MDI containing lecithin NF; MDI-OA: MDI containing oleic acid.

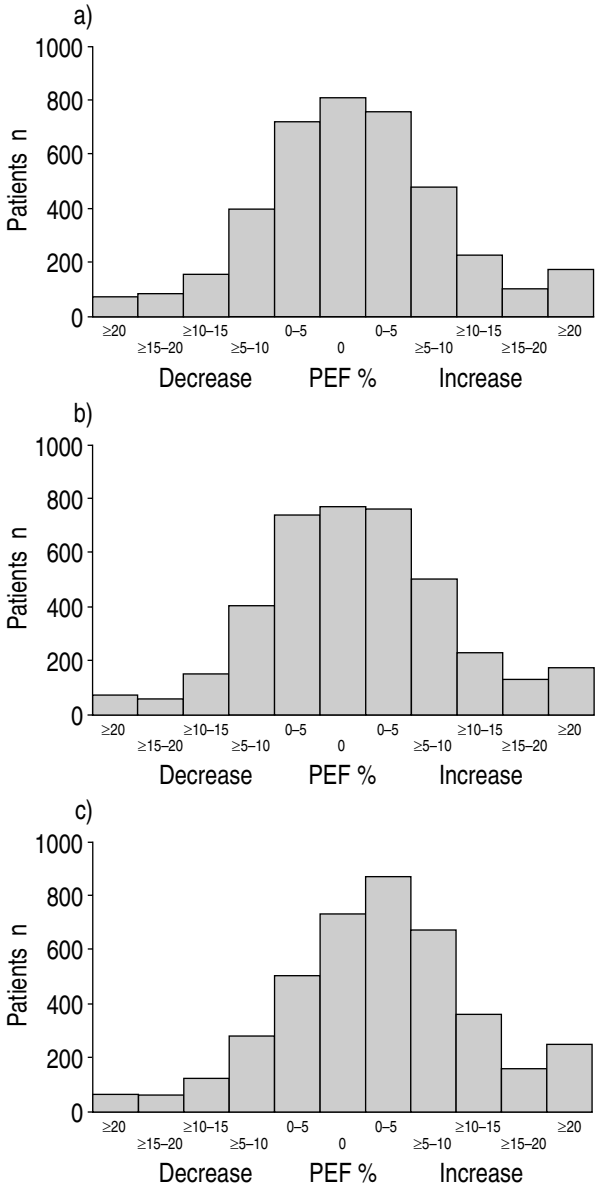

Fig. 1. – Frequency distribution of the percentage change in PEF 5 min postinhalation of two puffs from one of the following MDIs: a) MDI-OA; b) MDI-L; c) MDI-S. PEF: peak expiratory flow; MDI: metered-dose inhaler; MDI-OA: MDI containing oleic acid; MDI-L: MDI containing lecithin NF; MDI-S: MDI containing salmeterol xinafone (25 µg) and lecithin NF.

to -0.1%), or MDI-OA (p=0.011; 95% CI=-1.2% to -0.2%). There was no difference in the incidence of bronchoconstriction with MDI-L compared to MDI-OA.

A distribution plot of the peak flow changes for the three groups showed a skewed distribution (fig. 1). The median change for MDI-L and MDI-OA both centred around zero, whilst for MDI-S it was +2.3%. Interestingly, in all of the three groups, more patients showed a greater than 20% increase in PEF than had a greater than 20% decrease in PEF.

The incidence of bronchoconstriction analysed in relation to age and pretreatment PEF of the sample population is summarized in tables 2 and 3. The chance of bronchoconstriction occurring with MDI use increases with increasing age (p=0.005), (table 4). The evidence is strongest for patients aged over 80 yrs, where the chance of such an event is four times that for the youngest age category.

There is evidence of an increase in the chance of a bronchoconstricting event occurring as the pretreatment PEF decreases (p<0.001) (table 4). In particular, patients with a PEF of 50% or less of their predicted value have over four times the chance of experiencing bronchoconstriction with the use of the MDI than patients who have a PEF over 100% of their predicted value. There was no evidence of a significant interaction between age category and pretreatment PEF (p=0.25).

Although the reporting of physical signs of bronchoconstriction was not formally requested as part of the study, 20 (0.6%) patients reported actual symptoms

Table 2. – Table showing the percentage of patients experiencing drop in PEF of 20% or more, for the three treatment groups MDI-S, MDI-L and MDI-OA, in relation to the age of the patient

	% Patients ≥ 20% decrease PEF		
Age group yrs	MDI-S	MDI-L	MDI-OA
≤20	0.6	0.6	0.7
>20 ≤40	0.5	1.1	0.9
>40 ≤60	0.8	1.3	2.1
>60 ≤80	1.9	2.8	2.4
>80	3.0	5.8	3.8

For abbreviations see legend to table 1.

Table 3. – Table showing the percentage of patients experiencing a drop of PEF of 20% or more for the three inhalers MDI-S, MDI-L and MDI-OA with relation to the percentage predicted PEF measured prior to MDI use

PEF	% Patients ≥ 20% decrease PEF		
% pred	MDI-S	MDI-L	MDI-OA
≤50	2.8	4.4	5.9
>50 to 100	1.2	1.8	1.7
>100	0.4	0.9	0.8

For abbreviations see legend to table 1.

Table 4. – Table to show the odds ratio for comparisons of treatment, pretreatment PEF and age categories

Covariate	Ratio description	Odds ratio	95% CI
Treatment	MDI-L:MDI-S	1.60	(1.08–2.35)
	MDI-OA:MDI-S	1.64	(1.12–2.41)
Pretreatment PEF	>50–100%:>100%	1.92	(1.26–2.93)
category %	<50%:>100%	4.41	(2.67–7.27)
Age category	>20–40:≤20 yrs	1.41	(0.43–4.61)
	>40–60:≤20 yrs	2.03	(0.63–6.53)
	>60–80:≤20 yrs	2.81	(0.88–8.97)
	>80:≤20 yrs	4.11	(1.08–15.60)

95% CI: 95% confidence interval. For further abbreviations see legend to table 1.

of bronchoconstriction following the inhalation from the MDIs. This included nine patients from MDI-S, eight from MDI-OA and three from MDI-L groups. In addition, other events reported included coughing (two for MDI-S and one for MDI-L), choking sensation in the throat (one for MDI-S and one for MDI-L) and irritation of the throat (one for MDI-S and one for MDI-L). All the events resolved spontaneously or following bronchodilation.

Discussion

Although bronchoconstriction associated with MDI use has been well documented, this study attempted to estimate the incidence occurring within an adult asthmatic population. The occurrence of bronchoconstriction found for the three different MDIs, *i.e.* MDI-S, MDI-L and MDI-OA, has been shown in this study to be less than 2% of asthmatics.

The significantly lower incidence of bronchoconstriction seen with MDI-S is likely to be due to the bronchodilating effect of salmeterol xinafoate. Although the median time to show a 15% mean forced expiratory volume in one second (FEV_1) improvement has been reported to be 14 min [19], the bronchodilator activity of salmeterol xinafoate is sufficient to counteract some of the bronchoconstricting effect produced within the 5 min after inhalation. This is reflected by the skewed distribution of the PEF change seen with MDI-S (fig. 1), which showed many more patients having an increase rather than a decrease in PEF. This study suggests that it is not active medication which is the primary irritant causing bronchoconstriction but one or other of the inert constituents within the MDI. The dispersants, lecithin and oleic acid, have both been constituents within other MDI preparations which have previously been reported to cause bronchoconstriction [8, 20]. In addition, it is of interest to note that in most of the previous reports of bronchoconstriction the CFC, trichlorodifluoromethane has been present in the inhalers [8, 3, 13]. In one study, where bronchoconstriction was not shown, this particular CFC was absent from within the MDI [21]. In our study, trichlorodifluoromethane was present in all three MDIs. Although no definite relationship can be established, the dispersants lecithin and oleic acid, or the CFCs currently present in MDIs may be the source of the problem. One of the weaknesses of the study is the lack of ability to specifically distinguish between propellents or dispersants within the MDI, as the main cause of bronchoconstriction. What can be stated from the results of this study is that the combination of oleic acid and CFCs within the MDI is no more likely to produce bronchoconstriction than the lecithin NF and CFC combination.

A further consideration in discussing the results is the reproducibility of the peak flow measurements within the study and the impact any measurement errors may have had on estimating bronchoconstriction incidence. With short-term use, the mini-Wright peak flow meter is able to produce remarkably repeatable results that are within ±3% or 10 $l \cdot min^{-1}$ [22]. However, the mini-Wright meter, in common with other devices, has also been shown to have error profiles, particularly over the mid-range of PEF measurements. This can lead to errors in estimating PEF variability. Within this study, this could have led to an overestimation of bronchoconstriction for patients with low pretreatment PEF (<200 $l \cdot min^{-1}$) and an underestimation of bronchoconstriction in patients with high pretreatment PEF (>600 $l \cdot min^{-1}$). The size, randomized nature of the study and the similarity of the pretreatment PEF between the three groups all contributed to minimize any potential effect of the PEF meters.

The increase in incidence of bronchoconstriction with increasing age and severity of asthma, as reported in this study, is an important finding, especially as the factors appear to be independent of each other. Previous studies, which have investigated bronchial reactivity responses within adult asthmatic populations, have suggested that bronchial reactivity increases with increasing age and severity of disease [23– 25]. There seems, therefore, to be a greater potential for elderly and more severe asthmatics to be sensitive to nonspecific stimuli. An association of the bronchoconstriction caused by MDI use and the state of bronchial reactivity of the patient may, therefore, be an attractive hypothesis to put forward to explain the findings both of the age and pretreatment PEF effects seen in this study. However, further knowledge of the mechanism through which MDI-associated bronchoconstriction occurs is needed before such conclusions are made. A further point to consider in the interpretation of the results seen with increasing age and severity, is the influence that deep inspiration may have had on the incidence of bronchoconstriction with these two groups of patients. Deep inspiration has a variable effect on bronchial calibre, from one of bronchodilation to one of bronchoconstriction [26, 27]. A bronchoconstriction effect of deep inspiration seems to occur with an increasing pre-existing, spontaneous obstruction [27]. Therefore, this may explain, in part, the increased incidence in bronchoconstriction seen with increasing age and disease severity in this study, irrespective of the MDI used.

The single dose nature of this particular study makes any clinical interpretation of the findings difficult. It is impossible to know whether the 1.5% of patients who experienced bronchoconstriction following use of MDI-S, MDI-L or MDI-OA, would in fact experience such a reaction every time they used the MDI, or whether the bronchoconstricting response is unpredictable. Despite such uncertainties, clinicians should be aware that whilst paradoxical bronchoconstriction is not common, the possibility should be considered, especially in more elderly asthmatics and in patients with severe asthma.

Acknowledgement: The authors would like to thank all general practitioners who participated in the study.

References

1. Meeker DP, Wiedemann HP. Drug-induced bronchospasm. *Clin Chest* 1990; 11: 163–175.

2. Stanescu DC, van der Woestyne KP. Asthma attack induced by isoprenaline aerosols. *Respiration* 1972; 29: 532–537.
3. Shim C, Williams Jr MH. Cough and wheezing from beclomethasone aerosol. *Chest* 1987; 91(2): 207–209.
4. Snell NJC. Adverse reactions to inhaled drugs. *Respir Med* 1990; 84: 345–348.
5. Morley J, Sanjar S, Newth C. Viewpoint: untoward effects of beta-adrenoceptor agonists in asthma. *Eur Respir J* 1990; 3: 228–233.
6. Matzger E. Epinephrin by inhalation, for relief of attacks of bronchial asthma. *Cal West Med* 1935; 43: 226–227.
7. Reisman RE. Asthma induced by adrenergic aerosols. *Chest* 1973; 63 (Suppl.): 165.
8. Yarbrough J, Mansfield LE, Ting S. Metered-dose inhaler induced bronchospasm in asthmatic patients. *Ann Allergy* 1985; 55: 25–27.
9. Cocchetto D, Sykes RS, Spector S. Paradoxical bronchospasm after use of inhalation aerosols: a review of the literature. *J Asthma* 1991; 28(1): 49–53.
10. Ellwood R, Hogg J, Paré P. Airways response to osmolar challenge in asthma. *Am Rev Respir Dis* 1982; 125 (Suppl.): 61.
11. Beasley R, Raffety P, Holgate S. Adverse reactions to the nondrug constituents of nebuliser solutions. *Br J Clin Pharmacol* 1988; 25: 228–231.
12. Sterling GM, Batten JC. Effect of aerosol propellants and surfactants on airways resistance. *Thorax* 1969; 24: 28–231.
13. Bryant DH, Pepys J. Bronchial reactions to aerosol inhalant vehicle. *Br Med J* 1976; i: 1319–1320.
14. Charpin D, Beaupre A, Orehek J. Deep-inspiration induced bronchoconstriction: a mechanism for beclomethasone aerosol intolerance. *Eur J Respir Dis* 1983; 64: 494–497.
15. Ullman A, Svedmyr N. Salmeterol, a new long-acting, inhaled beta$_2$-adrenoceptor agonist: comparisons with salbutamol in adult asthmatic patients. *Thorax* 1988; 9: 674–678.
16. Dahl R, Earnshaw JS, Palmer JBD. Salmeterol: a four week study of long-acting, beta-adrenoceptor agonist for the treatment of reversible airways disease. *Eur Respir J* 1991; 4: 1178–1184.
17. Committee on Safety of Medicines. Current Problems. No. 31, June 1991.
18. Wilkinson JR, Roberts A, Bradding P, Holgate ST, Howarth PH. Paradoxical bronchoconstriction in asthmatic patients after salmeterol by metered-dose inhaler. *Br Med J* 1992; 305: 931–932.
19. Boyd G, Anderson K, Carter R. A 12 hour placebo-controlled comparison of the bronchodilator performance of salmeterol and albuterol. *Am Rev Respir Dis* 1990; 141 (4 part 2): A206.
20. Stanley SR. Possible reactions to soya lecithin in aerosols. *J Allergy Clin Immunol* 1991; 87(2): 600.
21. Shim CS, Williams Jr HM. Cough and wheezing from beclomethasone aerosol are absent after triamcinolone acetate. *Ann Intern Med* 1987; 106: 700–703.
22. Miller MR, Dickinson SA, Hitchings DJ. The accuracy of portable peak flow meters. *Thorax* 1992; 47: 904–909.
23. Lang DM, Hopp RJ, Bewtra AK, Nair NM, Watt GD, Townley RG. Distribution of methacholine inhalation challenge responses in a selected adult population. *J Allergy Clin Immunol* 1987; 79: 533–540.
24. Hopp RJ, Betwra A, Nair NM, Townley RG. The effect of age on methacholine response. *J Allergy Clin Immunol* 1985; 76: 609–613.
25. Burney PGJ, Britton JR, Chinn S, *et al*. Descriptive epidemiology of bronchial reactivity in an adult population: results from a community study. *Thorax* 1987; 42: 38–44.
26. Beaupré A, Badier M, Delpierre S, Orehek J, Grimaud C. Airway response of asthmatics to carbachol and to deep inspiration. *Eur J Respir Dis* 1983; 64: 108–112.
27. Lim TK, Ang SM, Rossing TH, Ingenito EP, Ingram RH. The effects of deep inhalation on maximal expiratory flow during intensive treatment of spontaneous asthmatic episodes. *Am Rev Respir Dis* 1989; 140: 340–343.