Eur Respir J 2002; 19: 246–251
DOI: 10.1183/09031936.02.00218402
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European Respiratory Journal
ISSN 0903-1936

Misuse of corticosteroid metered-dose inhaler is associated with decreased asthma stability

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ABSTRACT: This study assessed whether the improper use of pressurized metered-dose inhalers (pMDIs) is associated with decreased asthma control in asthmatics treated by inhaled corticosteroids (ICS).

General practitioners (GPs) included consecutive asthmatic outpatients treated by pMDI-administered ICS and on-demand, short-acting β_2-agonists. They measured an asthma instability score (AIS) based on daytime and nocturnal symptoms, exercise-induced dyspnoea, β_2-agonist usage, emergency-care visits and global perception of asthma control within the preceding month; the inhalation technique of the patient also was assessed.

GPs (n=915) included 4,078 adult asthmatics; 3,955 questionnaires were evaluable. pMDI was misused by 71% of patients, of which 47% was due to poor coordination. Asthma was less stable in pMDI misusers than in good users (AIS: 3.93 *versus* 2.86, $p<0.001$). Among misusers, asthma was less stable in poor coordinators (AIS: 4.38 *versus* 3.56 in good coordinators, $p<0.001$).

To conclude, misuse of pressurized metered-dose inhalers, which is mainly due to poor coordination, is frequent and associated with poorer asthma control in inhaled corticosteroid-treated asthmatics. This study highlights the importance of evaluating inhalation technique and providing appropriate education in all patients, especially before increasing inhaled corticosteroid dosage or adding other agents. The use of devices which alleviate coordination problems should be reinforced in pressurized metered-dose inhaler misusers.

Eur Respir J 2002; 19: 246–251.

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Keywords: Asthma control, inhaled corticosteroids, metered-dose inhaler, misuse, poor coordination

Received: February 22 2001
Accepted after revision August 9 2001

This work was supported in part by a grant from 3M Pharma, Cergy, France.

Asthma-related morbidity and costs remain high despite significant advances in the understanding, management and treatment of the disease. This may be due to several factors including increased asthma incidence, changes in environmental triggers, nonadherence of physicians to guidelines, noncompliance of patients, or failure of effective medications to reach their target at sufficient concentration because of misuse of inhalation devices. Indeed, inhalation remains the main route of administration for asthma therapy, since it allows drugs to reach high bronchial concentrations with low systemic bioavailability [1]. This is especially important for corticosteroids, which are the most effective maintenance therapy in asthma care [2].

Due to their high cost-effectiveness ratio [3], pressurized metered-dose inhalers (pMDIs) are the most commonly used inhalation devices. However, a number of surveys suggest that pMDIs are frequently misused: according to a review of 21 studies, the frequency of misuse ranges from 14–90%, with an estimated average of 50% [4, 5]. Misuse decreases lung deposition from 20% to 7% [6]; LINDGREN *et al.* [7] showed that the increase in forced expiratory volume in one second (FEV1) after inhalation of a short-acting β_2-agonist decreased by 30% in patients making inhalation errors, as compared to good pMDI users. When the drug used is an inhaled corticosteroid (ICS), the consequences of inhaler misuse have not been assessed and are less easily recognizable, since the expected benefits are not immediate and the disease is highly variable.

The present study was designed to determine if pMDI misuse is associated with increased asthma instability (as a marker of decreased corticosteroids efficacy) in patients treated with ICS.

Patients and methods

Subjects

General practitioners (GPs, n=915) were asked to include all consecutive consenting adult asthmatics (aged >15 yrs) who visited them, and had been treated for at least 3 months by regular ICS (500–1500 $\mu g \cdot day^{-1}$) and on-demand short-acting β_2-agonists, both administered by pMDI without holding chamber. The diagnosis of asthma had to be based on the operational definition provided by international guidelines [2]. Exclusion criteria were concomitant treatments within the previous 3 months with

long-acting β_2-agonists, long-term oral corticosteroids, β-blocking agents (eye-drops or by oral route) and theophylline.

Data collection

Patients answered a short questionnaire assessing their beliefs about their own inhalation technique, previous demonstration and assessment of inhalation technique, and perception of the suitability and efficacy of the inhalation device. Then, the physician completed a questionnaire on asthma instability within the previous month (table 1) and recorded the highest value of three peak expiratory flow rate (PEFR) measurements. Finally, patients were requested to take a puff of their usual short-acting β_2-agonist with their usual inhalation technique, which was observed and rated by the GP according to prespecified items (table 2). GPs had been previously taught by trained clinical research assistants on how to assess inhalation technique according to these items.

Asthma instability

An asthma instability score (AIS) was used which was developed by a panel of 11 experts (see Acknowledgement). Six items were selected because they were: 1) widely recommended and used for this purpose and 2) easy to collect in general practice. These items were: 1) daytime respiratory symptoms (chest discomfort, dyspnoea, cough, and wheezing); 2) asthma-related nocturnal awakenings; 3) exercise-induced asthma; 4) β_2-agonist usage; 5) serious exacerbations (*i.e.* requiring emergency medical intervention) and 6) global assessment by the GP of the evolution during the previous month. Then the panel determined the scoring range for each item, with the aim of detecting a clinically-significant difference for each one-point change. As indicated in table 1, this scoring system allowed the calculation of the global AIS, which could range from zero (best) to nine (worst).

Table 1. – Asthma instability score

Item (during the previous month)	Score
Respiratory symptoms frequency	
$<1\cdot week^{-1}$	0
$1\cdot week^{-1}$–$1\cdot day^{-1}$	1
$>1\cdot day^{-1}$	2
β_2-agonist usage	
$<1\cdot week^{-1}$	0
$1\cdot week^{-1}$–$1\cdot day^{-1}$	1
$>1\cdot day^{-1}$	2
Nocturnal awaking	
$<2\cdot month^{-1}$	0
$\geqslant 2\cdot month^{-1}$	1
Exercise-induced dyspnoea	
No exercise-induced dyspnoea	0
Presence of exercise-induced dyspnoea	1
Emergency-care visit	
No emergency-care visit	0
Without hospitalization	1
With hospitalization	2
Global perception of evolution	
Stable or improved	0
Unstable or worsened	1
Total	0–9

0: best asthma stability; 9: worst asthma stability.

Table 2. – Causes of metered-dose inhaler misuse

Cause of misuse	n	%
Omissions		
No removal of cap	16	0
Inhaler not held correctly	260	7
Device not actuated at the beginning of inspiration¶	748	19
No slow inspiratory flow	1348	34
No complete inspiration	919	23
>1 puff	739	19
No 5-s breath-holding period at the end of inspiration	1753	44
Errors		
Forced expiration	1077	27
No expiration	440	11
Inspiration by nose#	480	12
Actuation at the end of inspiration#	708	18
No inspiration#	224	6

#: one positive answer to at least one of these questions; ¶: a negative answer to this question defined poor coordination. n=3955.

Patient's inhalation technique

Inhalation technique was rated according to seven omissions and five errors (table 2) [1, 7–9]. Patients were classified as "misusers" if at least one error or omission was made. A subgroup of misusers was defined according to coordination between actuation and inhalation. Coordination was classified as "poor" if at least one of three potential errors was made (inspiration by nose, actuation at the end of inspiration, no inspiration) and/or if the device was not actuated at the beginning of inspiration.

Statistical analysis

Comparisons of quantitative variables (*i.e.* age, AIS and PEFR) between groups (*i.e.* between good users and poor users with and without poor coordination, and between educated and noneducated patients) were performed using a bilateral t-test for comparison of means. The sensitivity of the results to separate removal of each item of the AIS was studied and the relationship between each potential error or omission in inhalation technique and AIS was assessed. Categorical variables (*i.e.* sex, age range, and cause of medical visit) were compared between the groups studied, using table analysis by Pearson's Chi-squared test [10]. Correlations between quantitative variables (*i.e.* between AIS and PEFR, and between AIS and age) were studied by linear regression analysis. Values of $p<0.05$ were considered statistically significant.

Data are reported as mean±SEM unless otherwise indicated.

Results

Of the 4,198 questionnaires completed, 120 (2.8%) were excluded from analysis because of patient's ineligibility (age <15 yrs in five patients, recent use of long-acting β_2-agonists in 115). In the remaining population (n=4,078), 2,179 were males (54%) and 1,869 were females (46%), with a mean age of 46.3±19.3 yrs. PEFR was available in 3,055 patients (75% of eligible subjects), with a mean value of 382±106.8 $L \cdot min^{-1}$ (range: 105–800), *i.e.* 72.8±19.0% of predicted. The cause leading the patient to seek medical advice was first visit in 102 cases (3%), routine scheduled visit in 2,932 cases (70%), asthma worsening in 789 cases (20%) and an acute exacerbation in 149 cases (4%). Short-acting β_2-agonists had been taken within 4 h prior to the visit by 38% of patients.

Pressurized metered-dose inhaler misuse

Of the 3,955 patients in whom all corresponding items were documented (97% of the eligible population), 2,791 (71%) were considered as poor users; among them 1,320 (33%) were poor coordinators (corresponding to 47% of poor users). Among misusers, 78% made >1 error or omission in inhalation technique. Only 15% of poor users and 23% of poor coordinators self-rated their technique of inhalation as "poor" or "very poor". Causes of poor inhalation technique are given in table 2. The frequency of pMDI misuse increased with age and was 61.0% between 15–30 yrs, 70.0% between 30–60 yrs, 77.2% between 60–75 yrs, and 85.9% in patients >75 yrs (p<0.00001). There was no difference in the frequency of misuse between males and females (69.4 *versus* 72.0%, respectively; p=NS), although the frequency of poor coordination was slightly higher in females (35.9 *versus* 30.4% in males, p=0.0002).

Effect of prior education on inhalation technique and asthma instability

Before the visit, 84% of patients had been shown how to use their inhaler and inhalation technique had been checked in 68%. Misuse was less frequent in subjects in whom these two steps of education had been performed (66.5% *versus* 86.4% in subjects who received no education; p<0.0001). There was no difference between educated and noneducated patients in terms of AIS (3.73±0.11 *versus* 3.61±0.05; p=0.41) but PEFR was slightly but significantly lower in noneducated patients (70.4±0.4 *versus* 72.9±1.0; p=0.02). Worsened asthma condition was a more frequent cause of medical visit (3.3 *versus* 6.2%; p=0.005) in noneducated patients.

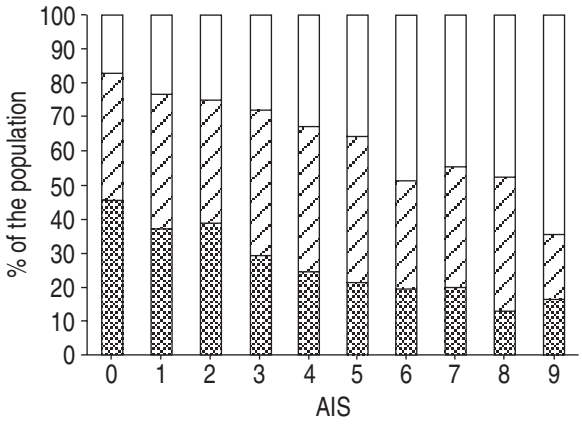

Fig. 1. – Distribution of asthma instability score (AIS) according to inhalation technique and coordination. □: misusers, poor coordinators; ▨: misusers, good coordinators; ■: good users. n=3709 (91% of the eligible population). Analysis of variance: p<0.0001.

Relationship between pressurized metered-dose inhaler misuse, cause of medical visit and asthma instability

PEFR correlated to AIS (r=0.33, p<0.00001) and was lower in misusers (71.6±0.4% of predicted) and poor coordinators (70.1±0.6%) than in good users (75.5±0.6%, p<0.0001 for each comparison). The cause of medical visit in good users and misusers without and with poor coordination is given in table 3. Medical visits for worsened asthma condition or emergency visits were more frequent in misusers with poor coordination, than in misusers without poor coordination or good users (p<0.00001).

AIS and evaluation of inhalation technique were both available in 3,709 patients (91% of the eligible population). The distribution of the AIS in good users and misusers with and without poor coordination is given in figure 1. The mean AIS was higher in

Table 3. – Cause of medical visit, β_2-agonist usage, recent evolution of asthma and emergency-care visit during the previous month according to inhalation technique and coordination

	Good users	Misusers without poor coordination	Misusers with poor coordination
Cause of medical visit			
Routine or first visit	81	77	69
Emergency or worsened asthma	19	24	31
β_2-agonist usage $>1 \cdot day^{-1}$	26	36	42
Evolution rated as unstable or worsened	36	46	62

Data are presented as percentages. p<0.002 for all comparisons.

misusers than in good users and, among misusers, the mean AIS was higher in poor coordinators (table 4). In misusers as compared to good users, and in misusers with poor coordination as compared to misusers without poor coordination, the greater instability of asthma was reflected, in particular, by more frequent β_2-agonist use, recent worsening of asthma and occurrence of serious exacerbations (table 3, $p<0.01$ for all comparisons).

There were significant differences in AIS according to the presence or absence of each single error or omission in inhalation technique ($p=0.03$ for cap removal and $p<0.00001$ for all others). Linear regression analysis showed that the number of errors in inhalation technique, as described in figure 2, correlated to the AIS ($r=0.3$, $p<0.0001$). According to stepwise analysis, errors or omissions that independently correlated to the AIS, were upside-down metered-dose inhaler holding, forced expiration prior to inhalation, inappropriate timing of device actuation including actuation at the end of inspiration, too high inspiratory flow rate, incomplete inspiration, double actuation and lack of apnoea following inspiration.

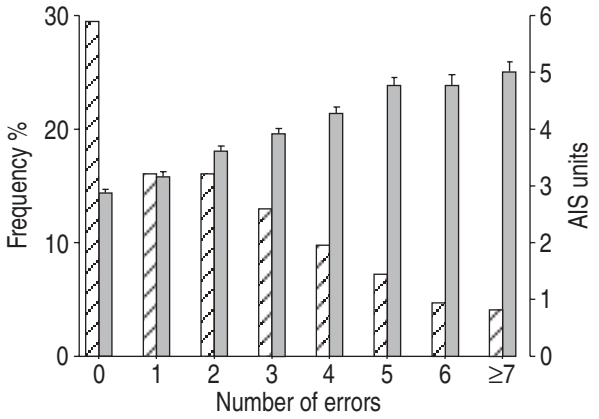

Fig. 2. – Frequency distribution of the number of errors or omissions in inhalation technique (left axis: ▨) and relationship between this number and AIS (mean±SEM, right axis: ■). Correlation between number of errors and AIS (linear regression analysis): $r=0.3$, $p<0.0001$.

Sensitivity of the results to changes in asthma instability score items

Separate removal of each individual item of the AIS did not affect the relationship between this score and inhaler misuse with or without poor coordination (t-tests, $p<0.0001$ for all comparisons). Similarly, it did not alter the correlation of this score with PEFR ($p<0.0001$ for all regression analyses). Each single item of the AIS was influenced by misuse and especially poor coordination ($p<0.0001$ for all comparisons).

Discussion

In adult asthmatic patients treated with ICS and visiting their GP, the proportion of pMDI misusers was high and increased with age. Misuse and more specifically poor coordination were strongly associated with asthma instability. This suggests that the decrease in lung deposition which is associated with pMDI misuse reduces the clinical efficacy of ICS and impairs asthma control.

Several points have to be considered when interpreting the results. Firstly, participating GPs were volunteers, so that their interest in asthma might have induced a better knowledge of inhalation devices and a better education of their patients. Similarly, patients had to give their consent before participation in the study, which may influence the frequency of pMDI misuse. However, these potential bias would have led to underestimation of the frequency of pMDI misuse. This frequency was high (71%) but very similar to what has been found in other studies [4, 11–14]. Indeed, this study is, to the best of the authors' knowledge, the largest to assess the frequency of pMDI misuse.

Secondly, potential confounding factors were not considered, such as baseline disease severity, poor compliance, insufficient asthma treatment including inadequate ICS dosage, diagnostic errors, comorbid heart or respiratory illnesses, poor control of environmental triggers such as allergen exposure. However, the large size of the studied sample and the magnitude and consistency of the difference in asthma instability between pMDI misusers and good users make it unlikely that these differences were due only to confounding factors; in addition, all AIS items were influenced by misuse and especially poor coordination, and the relationship between misuse, poor coordination and AIS was insensitive to separate removal of each single item of the AIS: this suggests that misuse and especially poor coordination are very important factors for asthma control.

Greater asthma instability in patients treated by ICS and showing poor use of their inhaler might be explained by a direct mechanism (the failure of medication to reach the bronchi at adequate concentration)

Table 4. – Mean asthma instability score according to inhalation technique and coordination

	Good users	Misusers (all)	Misusers without poor coordination	Misusers with poor coordination
Subjects n	2629	1427	1202	
% of total population	29	71	39	32
AIS	2.87±0.07#	3.93±0.05#	3.56±0.06#	4.38±0.07#

Data are presented as mean±SEM unless otherwise stated. AIS: asthma instability score. #: $p<0.0001$.

as well as an indirect one (lower compliance due to decreased efficacy). Such a vicious circle is quite classical with treatments of chronic diseases requiring a strict compliance: breaking it down is of utmost importance in a potentially fatal and resource-consuming disease such as asthma. Compliance could not be reliably assessed in this study since it was cross-sectional; prospective trials will be required to study its relationship with misuse.

The strict criteria used to define good use of pMDIs may partly account for the high frequency of misuse, however, these criteria are based on data from scintigraphic deposition studies [6, 8, 9], and, as outlined earlier, a figure of 71% remains within the range found by other sources [4, 11–14]. In addition, only a low proportion of misusers (22%) had only one error or omission and each single error was associated with asthma instability, which increased with the number of errors. The high frequency of poor coordination (47%) among possible causes of misuse is also in accordance with the results of previous surveys [4], as is the increase in misuse with age [12, 15]. The association between poor coordination and worse asthma control in misusers suggests that one of the first aims of research on inhalation devices should be to alleviate coordination problems.

The impact of improper pMDI usage on the lung deposition of inhaled agents has been clearly demonstrated in numerous well-designed studies. Altogether, these studies found a 50–66% reduction in lung deposition in pMDI misusers [6, 8, 16]. The clinical consequences of this decrease in lung deposition have been easy to demonstrate with bronchodilators, since an immediate indicator of drug effect does exist and is easy to measure (*i.e.*, the magnitude of bronchodilation, which decreases by 30% with pMDI misuse) [7].

The picture is more complicated when the treatment targets a long-term effect and when the disease is intrinsically variable. In the present study, asthma instability was proposed as a potential indicator of the hazards of faulty inhaler technique. Because asthma can be severe but controlled, or moderate but unstable (depending on the adequacy of administered treatments) [2, 17], assessing instability appeared more relevant than assessing severity. The authors developed the AIS since there was no generally accepted and validated measure for asthma instability at the time of the current study. Although this score allowed the demonstration, for the first time, of a relationship between corticosteroid pMDI misuse and poor asthma control, the significance of this result could be questioned, since the AIS had not been formally validated before its use in this study. However, this score was developed by an expert panel using items which were widely recommended and used for assessment of asthma control, and which were all influenced by misuse and poor coordination; three out of six of the AIS items were used to define asthma control in the study by Reddel *et al.* [18], and four are part of the six-item asthma control questionnaire (ACQ) which has recently been transversally and longitudinally validated by Juniper *et al.* [19] in 50 patients. AIS items that are not included in the ACQ are emergency-care visits and global assessment of evolution by the patient. Conversely, ACQ but not AIS includes wheezing and FEV_1. Other main differences between the AIS and the ACQ are the duration of retrospective assessment (1 week for the ACQ and 1 month for the AIS) and the way of scoring each item (six-point scales for the ACQ, two or three-point scales for the AIS). Although not formally tested, the discriminant properties of the AIS are suggested by its correlation with PEFR, which was highly significant although of low magnitude, as could be expected in ICS-treated patients. If this score was to be used in longitudinal studies, its responsiveness to change should be determined.

Finally, a one-point mean difference in AIS was found between good and poor users, corresponding to 11% of the maximal total AIS (*i.e.* nine points). Interestingly, the difference in variation of the ACQ between stable and unstable patients found by Juniper *et al.* [19] was 0.72, corresponding to 12% of the maximal total ACQ (*i.e.* six points). This suggests that a one-point difference in the AIS is indeed of clinical significance.

Fewer misusers than good users had received education on inhalation technique, which suggests that education is effective at improving inhaler technique. However, there was no significant direct relationship between education and AIS, which is most likely due to the fact that education is not always successful (errors are corrected in only 50% of poor users, 50% of whom return to their "bad habits" within a few weeks), and that misuse is obviously not the only factor that influences asthma control.

Another striking finding was the lack of awareness in poor users of their difficulties with pMDI inhalation technique, only 15% rating their pMDI use as "poor" or "very poor". As emphasized by others [20], this highlights the need for progress in asthmatics' education and about the correct use of inhalers.

To conclude, it is clearly important to evaluate patient inhalation technique, and especially coordination errors, before increasing inhaled corticosteroids dosage or adding long-acting β_2-agonists in patients in whom asthma is poorly controlled. Use of devices that make inhalation technique easier, such as holding chambers, breath-actuated devices and dry-powder inhalers should be reinforced in pressurized metered-dose inhaler misusers. This strategy, which is already recommended by international guidelines on asthma, should be more extensively implemented to limit the cost and side-effects of unnecessary additional treatments. The beneficial effect of improvement in inhalation technique or change in inhalation device, on asthma control, now needs to be demonstrated in prospective trials.

Acknowledgement. The authors wish to thank P. Chanez, B. Crestani, R. Dubost, A. Magnan, M. Murris-Espin, C. Pannelier, M. Pérol, T. Perez, O. Sitbon, C. Thiriet, M. Tunon de Lara for their help in designing the asthma instability score or organizing data collection.

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