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Dry Powder Inhalers: Which Factors Determine the Frequency of Handling Errors?

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Key Words
Dry powder inhalers · Handling errors · Asthma · Chronic obstructive pulmonary disease

Abstract
Background: Dry powder inhalers are often used ineffectively, resulting in a poor level of disease control. ***Objectives:*** To determine how often essential mistakes are made in the use of Aerolizer®, Discus®, HandiHaler® and Turbuhaler® and to study the effects of age, severity of airflow obstruction and previous training in inhalational technique by medical personnel on the error rate. ***Methods:*** Two hundred and twenty-four newly referred outpatients (age 55.1 ± 20 years) were asked how they had been acquainted with the inhaler and to demonstrate their inhalational technique. ***Results:*** The inhaler-specific error rates were as follows: Aerolizer 9.1%, Discus 26.7%, HandiHaler 53.1% and Turbuhaler 34.9%. Compared to Aerolizer, the odds ratio of an ineffective inhalation was higher for HandiHaler (9.82, $p < 0.01$) and Turbuhaler (4.84, $p < 0.05$). The error rate increased with age and with the severity of airway obstruction ($p < 0.01$). When training had been given as opposed to no training, the odds ratio of ineffective inhalation was 0.22 ($p < 0.01$). If Turbuhaler is used, the estimated risks range from 9.8% in an 18-year-old patient with normal lung function and previous training to 83.2% in an 80-year-old patient with moderate or severe obstruction who had not received any training. ***Conclusions:*** Dry powder inhalers are useful in the management of younger patients with normal lung function or mild airway obstruction. In older patients with advanced chronic obstructive pulmonary disease, the risk of ineffective inhalation remains high despite training in inhalational technique. A metered-dose inhaler with a spacer might be a valuable treatment alternative in a substantial proportion of these patients.

Introduction

Topically inhaled drugs play a central role in the management of patients with asthma or chronic obstructive pulmonary disease (COPD). Treatment guidelines focus on pharmaceutically based strategies, but little attention is given to the way inhalers are handled by the patients. The fact that the best drugs remain ineffective if not deposited to the lung due to poor inhalational technique is not adequately recognised [1]. Few impressions in clinical practice are as depressing as observing patients who use

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expensive inhalers in a manner that makes endobronchial deposition of the drug impossible. Fink and Rubin [2] estimate the annual direct loss due to handling errors at 5–7 billion USD, under the premise that 28–68% of patients do not use their inhalers correctly. Lack of effect due to handling flaws fosters a cost-driving polypragmasy. High costs arise if insufficient deposition of the medication to the lung leads to exacerbation of the disease or if an oral long-term steroid treatment is initiated under the false assumption that an adequate asthma control cannot be achieved with inhalational treatment [3]. Dry powder inhalers have been developed to overcome the difficulties in use of metered-dose inhalers and are often prescribed with the hope of a more user-friendly and more predictable therapy.

This observational study examines the frequency of handling errors in the use of Aerolizer®, Discus®, HandiHaler® and Turbuhaler® and the influence of age, degree of lung function impairment and instruction in inhalational technique by health care professionals on the error rate.

Table 1. Handling errors defined a priori as essential

Aerolizer:
Not closing the mouthpiece until a click is heard.
Not piercing the capsule.
Not releasing the squeezed piercing buttons throughout inhalation.
Discus:
Not sliding back the lever until a click is heard.
Sliding back the lever after inhalation is started.
HandiHaler:
Not closing the mouthpiece until a click is heard.
Not piercing the capsule.
Not releasing the pressed piercing button throughout inhalation.
Turbuhaler:
Not holding inhaler upright when twisting the grip (tolerance ±45°).
Not twisting the grip in both directions as far as it will go until a click is heard before starting inhalation.
All inhalers:
Insufficient inspiratory flow.

Patients and Methods

The study was conducted on newly referred outpatients reporting the use of 1 or several of the above-mentioned inhalers. The evaluation was restricted to these inhalers because the number of patients using other devices was too small for statistical analysis.

The patients were first asked how they were familiarised with the inhaler. The following differentiation was made: no training in inhalational technique but instead reference to the package insert or to other written information, training by a chest physician, or training by another health care provider. Next, the patients were asked to demonstrate their inhalational technique with an empty inhaler, for which they were provided empty capsules for Aerolizer and HandiHaler. Each patient had only one opportunity to demonstrate his or her inhalational technique.

The inhalational technique was assessed by the same observer in each case. Inhaler-specific operating errors that make significant deposition of the medication to the lung impossible were defined a priori as 'essential' (table 1).

Other crucial errors that had not been anticipated were observed during the course of the study, and classified as essential as well. This category included exhalation into the device instead of inhalation, device not taken into the mouth, mouthpiece of Turbuhaler cannot be sealed by the lips due to facial paralysis, Discus knocked on the table with the mouthpiece facing downwards after sliding back the lever before inhalation, and inhalation through the grooves of the lever instead of the mouthpiece of Discus. The technique was classified as ineffective if at least 1 essential error was made.

Ineffective inhalation attempts were classified as 'technically incorrect' or 'incorrect due to insufficient inspiratory flow'. The inspiratory flow necessary for sufficient deposition of the medication is inhaler specific. If the inspiratory flow with the test device appeared to be insufficient during the demonstration with Aerolizer, Discus or Turbuhaler, this was verified by measurement of peak inspiratory flow using the In-Check® device (Clement Clark, Essex, UK) [4, 5]. Since a flow measuring device was not available for HandiHaler, insufficient inspiratory flow was assumed if a weak inhalation did not cause an audible rattle of the capsule in the inhaler.

The disease present was classified as asthma, COPD or other diseases. The degree of airway obstruction was stratified into 4 levels of severity based on the forced expiratory volume in 1 s as percentage of the predicted values: no obstruction (>80%), mild (60–80%), moderate (40–60%) or severe (<40%). The COPD patients were also classified according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages.

The study was given approval by the ethics committee of the General Medical Council of Baden-Württemberg.

Statistics

Generalised estimation equations (GEE), which allow an evaluation of dependent observations, were applied to account for the use of more than 1 inhaler by individual patients [6–8]. GEE models were fitted to investigate the effect of training (no instruction versus instruction) and the type of training (no instruction versus instruction by a chest physician versus instruction by other medical personnel) on the error rate. It was not possible to fit a GEE model for the relationship between effective inhalation and inhaler type due to convergence problems. Instead, 1 inhaler was selected randomly from among the patients using several inhalers and evaluated together with the data of patients who used a single

Table 2. Distribution of the inhalers among the patient groups

Inhaler	All patients	Asthma	COPD	Other diseases
Aerolizer	22 (8.8)	14 (10.9)	5 (6.1)	3 (7.9)
Discus	86 (34.5)	48 (37.2)	27 (32.9)	11 (29.0)
HandiHaler	32 (12.9)	9 (7.0)	20 (24.4)	3 (7.9)
Turbuhaler	109 (43.8)	58 (45.0)	30 (36.6)	21 (55.3)

Figures in parentheses are percentages.

inhaler by logistic regression analysis. The influence of the inhaler on the type of handling error (technically incorrect versus incorrect due to insufficient inspiratory flow) was investigated using a mixed effects regression model. The dependence of effective inhalation on sex and age was investigated with the χ^2 test and by means of logistic regression analysis, respectively. The dependence of effective inhalation on the number of inhalers used was investigated with the χ^2 test. One patient using 2 inhalers and demonstrating effective as well as ineffective inhalation had to be excluded from this analysis.

The relationship between effective inhalation and severity of airway obstruction was investigated using the Cochran-Armitage trend test. One patient in the 'other diseases' group had to be excluded from this analysis as spirometry was not possible due to lack of cooperation. The effects of age, severity of obstruction, inhaler type and training on ineffective inhalation were investigated using a mixed effects regression model for binary data. The estimations of the regression coefficients were used in a risk prediction model for estimating patient- and inhaler-specific risks of ineffective inhalation. The risk prediction model had to be restricted to Discus and Turbuhaler because the numbers of patients using Aerolizer and HandiHaler were too low for analysis.

The statistical analysis was performed using SAS, version 9.1. The following procedures were used: univariate, freq, logistic, nlmixed, genmod and glimmix (June 2006 release). Due to the exploratory nature of the study, no adjustment for multiple testing was made. All tests were performed at a significance level of 0.05.

Results

A total of 224 consecutive patients (124 male, 100 female) with a mean age of 55.1 ± 20.1 years (range 6.1–84.5) were studied. Neither asthma nor COPD were present in 36 patients (16.1%). Asthma was present in 121 patients (54%). COPD was found in 67 patients (29.9%), with the following distribution according to the GOLD classification: 1 patient (1.5%) GOLD I, 32 (47.8%) patients GOLD II, 12 patients (17.9%) GOLD III and 22 patients (32.9%) GOLD IV. The COPD patients were older than the asthmatics (average age 69.5 ± 9.4 vs. 48.1 ± 20.5 years; $p < 0.01$) and showed a higher degree of obstruction.

There were 249 inhalers used by 224 patients. A total of 24 patients used more than 1 inhaler; 23 patients used 2 inhalers and 1 patient used 3 inhalers. The distribution of the inhalers among the patient groups is shown in table 2.

Ineffective inhalation was found to be present in 80 (32.1%) of the 249 examinations and in 30.9% of the patients. The error rate was not significantly lower if only 1 inhaler was used than if multiple inhalers were used (29.5 vs. 43.4%, $p = 0.17$). No significant difference was observed between males and females (26.0 vs. 37.0%, $p = 0.08$). The following inhaler-specific error rates were found: Aerolizer 9.1%, Discus 26.7%, HandiHaler 53.1% and Turbuhaler 34.9%. The error rate was significantly higher with HandiHaler and Turbuhaler than with Aerolizer. The odds ratio for ineffective inhalation was 9.82 (95% CI 1.84–52.38, $p < 0.01$) for HandiHaler and 4.84 (95% CI 1.06–22.02, $p < 0.05$) for Turbuhaler compared to Aerolizer.

The inhalers did not differ with respect to the distribution of the type of handling error (insufficient inspiratory flow with correct technical handling vs. incorrect technical handling with adequate inspiratory flow). The error rate increased with age ($p < 0.01$). The relationship is shown in figure 1. The effect of age on the error rate remained significant even after adjustment for severity of obstruction and type of training ($p < 0.05$). The subgroup analyses of the individual inhalers showed a correlation between increased age (above 60 years vs. below 60 years) and increased error rate with Discus (5.3 vs. 43.8%, $p < 0.01$, odds ratio 0.07, 95% CI 0.02–0.33) and Turbuhaler (25.4 vs. 46.0%, $p < 0.05$, odds ratio 0.40, 95% CI 0.18–0.90).

The error rate increased with the severity of obstruction, as shown in figure 2. The error rates were 25.0% with normal lung function and 63.6% with severe obstruction. This difference was significant in the entire group ($p < 0.01$) as well as in the COPD subgroup ($p < 0.05$). A similar picture was seen with reference to the GOLD classification ($p < 0.01$). A significant relation ($p < 0.01$) was seen between the severity of obstruction and the error rate with Turbuhaler. No significant correlation could be demonstrated with Discus, HandiHaler or Aerolizer.

Amongst patients who were treated with Aerolizer, 63.6% reported that they had been trained in inhalational technique by medical personnel. The percentages for Discus, HandiHaler and Turbuhaler were 65.1, 71.8 and 73.4%, respectively. An error rate of 52.6% was found in

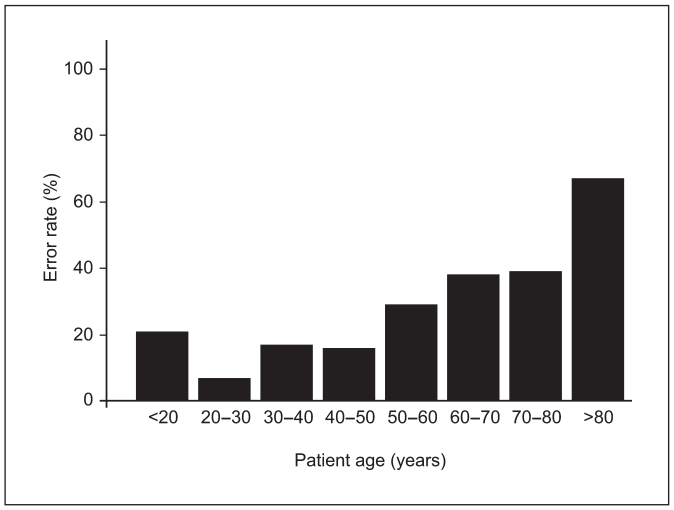

Fig. 1. Frequency of essential handling errors among 223 patients using Aerolizer, Discus, HandiHaler or Turbuhaler stratified by age. One patient using 2 inhalers and demonstrating both effective and ineffective inhalation was excluded from this analysis.

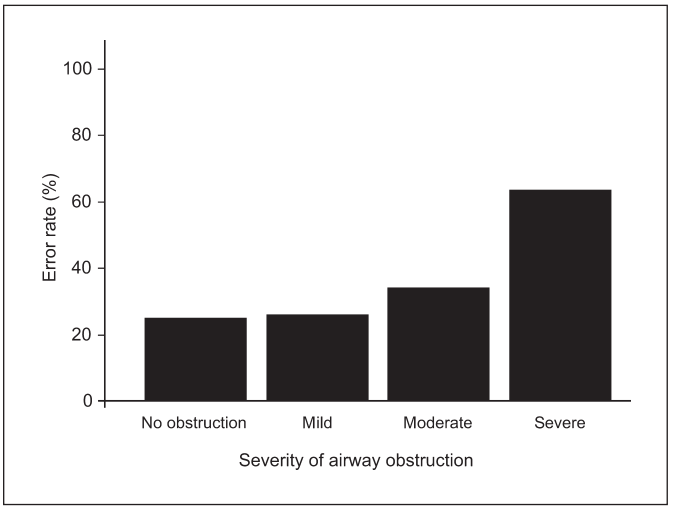

Fig. 2. Frequency of essential handling errors among 222 patients using Aerolizer, Discus, HandiHaler or Turbuhaler stratified by the severity of airway obstruction. Two patients were excluded from this analysis; 1 patient using 2 inhalers demonstrated both effective and ineffective inhalation, in 1 patient, spirometry was impossible due to lack of cooperation.

the group of 76 patients who had not received any instruction, in contrast to only 23.1% of the trained patients who made essential errors (odds ratio 0.22, 95% CI 0.12–0.41, $p < 0.01$). The positive effect of training was confirmed for Discus (odds ratio 0.17, 95% CI 0.06–0.47, $p < 0.01$) and Turbuhaler (odds ratio 0.20, 95% CI 0.08–0.50, $p < 0.01$). No such relation was seen for HandiHaler and Aerolizer. The odds of ineffective inhalation after training by a chest physician did not differ significantly from the odds after training by other medical personnel.

Figures 3 and 4 illustrate the effects of training, age and lung function on the risk of ineffective inhalation among patients treated with Turbuhaler and Discus as estimated by the risk prediction model.

Discussion

A number of dry powder inhalers with different modes of operation are available. The variety of potential handling flaws is difficult for the prescribing physician to appraise, especially if he or she is not specialised in respiratory medicine [9–11]. Pharmaceutical manufacturers have been involved in many publications on this subject, with their inhalers generally being presented in favourable terms and as easy to use [12–19].

This does not always accord with clinical experience, as can be seen from our study. A substantial proportion of patients handled their inhalers poorly. Patients using Aerolizer made significantly fewer mistakes than those using HandiHaler or Turbuhaler. Hesselink et al. [20] found an error rate of 31.4% with Turbuhaler in patients with asthma or COPD, which is close to the value of 34.9% found in our study and in keeping with the data of van der Palen et al. [21]. Melani et al. [22] found essential error rates of 17, 23 and 24% for Aerolizer, Discus and Turbuhaler, respectively. The error rate with HandiHaler was higher than could be expected from the data in the literature [14, 23]. Incorrect use of HandiHaler was mostly due to the fact that the button on the side was either not pressed at all or depressed continuously during inhalation. The most common mistake that was made in using Discus was sliding back the lever during inhalation rather than before inhalation. Errors in using Turbuhaler were mostly related to the loading process which is position sensitive. Gender-specific differences were not found, which is in line with the results of Melani et al. [22]. Van der Palen [24] found an increased error rate when more than 1 inhaler was used. This could not be shown in our study – possibly due to the relatively small number of patients who used several inhalers.

It is difficult to compare studies on error rates owing to the lack of a common definition of error. Our study only took into account essential errors because non-es-

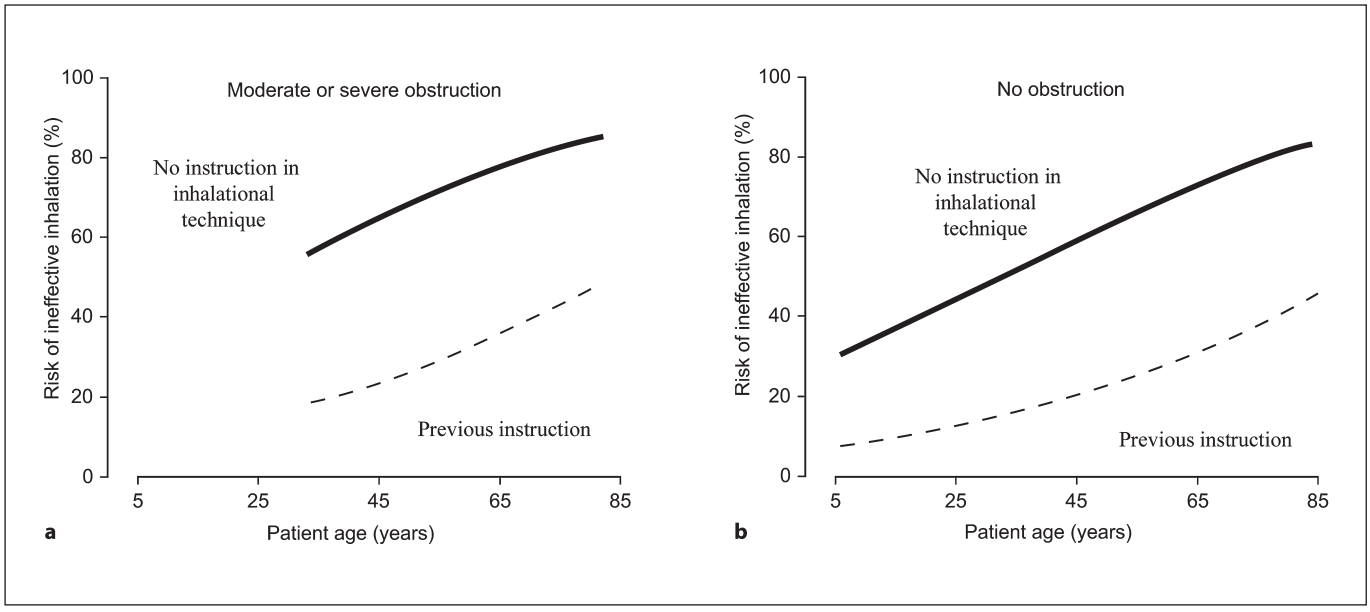

Fig. 3. Risk of ineffective inhalation among patients with and without prior instruction in inhalational technique who were treated with Turbuhaler, expressed as a function of age. **a** Patients with moderate or severe obstruction (n = 29; mean age 67.2 ± 11.7 years, range 33.2–82.3). The 2 lung function categories were pooled to 1 stratum because the number of patients who had severe obstruction and had not received instruction in inhaler use was too low for statistical analysis. **b** Patients with no obstruction (n = 63; mean age 45.2 ± 20.4 years, range 6.5–84.5). Prior instruction in inhaler use by medical personnel is associated with a reduced risk of ineffective inhalation.

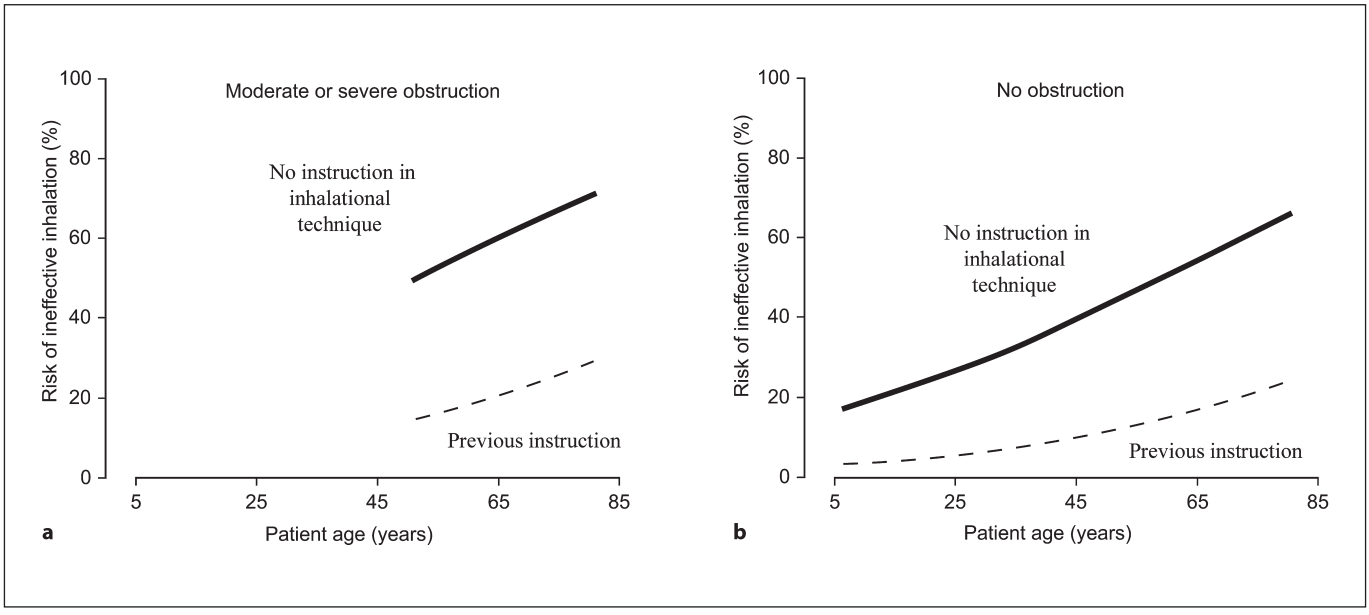

Fig. 4. Risk of ineffective inhalation among patients with and without prior instruction in inhalational technique who were treated with Discus, expressed as a function of age. **a** Patients with moderate or severe obstruction (n = 21; mean age 69.7 ± 10.3 years, range 51.2–81.6). **b** Patients with no obstruction (n = 45; mean age 47.1 ± 21.5 years, range 6.1–80.9).

sential errors are of uncertain clinical significance. The error rate is therefore lower than in studies in which the inclusion of non-essential errors created a wider range of potential handling errors. Inhalational flow with Aerolizer, Discus or Turbuhaler was measured with the In-Check device in case of doubt. According to the literature, an inspiratory flow rate of 20 l/min is sufficient for effective inhalation when using HandiHaler [14, 23]. Since a device to quantify the inspiratory flow rate was not available, sufficient inspiratory flow was assumed with HandiHaler if the capsule rattled audibly. This less stringent criterion is a potential bias against the other inhalers in which the peak inspiratory flow was verified with the InCheck device.

A lack of inhaler skills amongst many health care professionals has been repeatedly described for more than a decade [2, 25–29]. Fink and Rubin [2] have pointed out that 39–67% of nurses, physicians and respiratory therapists are unable to provide an adequate description of how to perform crucial steps for using inhalers. We anticipated that these deficiencies would entail an improper inhalational technique being taught to patients and did not expect that instruction by medical personnel had such a positive impact on the error rate. Our findings suggest that many health care professionals do know how to instruct their patients properly in the use of the inhalers investigated. It is to be assumed that medical personnel who do not instruct in inhaler use are less knowledgeable about this subject than those who provide instruction. The experience gained during this study showed that many caregivers must improve their knowledge and adopt modern teaching techniques to meet the requirements of their patients. For instance, a poor level of asthma control cannot be attributed to shortcomings of a dry powder inhaler if the device is prescribed without any instruction to a patient who cannot seal the mouthpiece with his lips due to facial paralysis. The subgroup analyses suggest that the error rates with Discus and Turbuhaler can be significantly reduced by appropriate training. High-quality training devices are available. Simple but fatal errors could be avoided in many cases by their use. The finding that approximately one fourth of the patients treated with Turbuhaler and nearly one third of those treated with Discus were only referred to the package insert shows that these training devices are not used to the necessary extent. Their routine use would be an efficient way to prevent handling errors from the very onset of therapy because an alternative inhalational system could be selected for patients who are unable to handle the test device properly.

Since the introduction of new dry powder devices will continue, a growing number of devices will contain the same chemical entity. Medical personnel do not have sufficient time to become adequately familiar with the strengths, weaknesses and pitfalls of new developments, so that they cannot teach the patients the optimal use. As management of chronic airway disease is 10% medication and 90% education [2], the proliferation of inhaler types may become disadvantageous for the quality of care. Physicians in general practice should limit their selection to a small number of inhaler types whose operating principles they can study in detail.

The economic pressure to prescribe less expensive inhalers and issue prescriptions without specifying brands is increasing. We know of several incidents in which the pharmacist substituted a patient's regular dry powder inhaler with a less expensive but unfamiliar device. Pharmacists often have deficiencies of knowledge regarding inhaler use [25]. For this reason many pharmacists are neither interested nor in a position to offer training in use of devices. Consistent with this assumption is the experience that among the 224 patients of this study only 1 patient reported receiving instruction in inhalational technique at the pharmacy. Theoretical cost benefits which might be expected from switching to a nominally less expensive inhaler are often outweighed by the need for unscheduled consultations and reissuing prescriptions. In order to avoid this waste of resources, the prescribing physician should specify the type of inhaler to be dispensed. Matching the appropriate device for the individual patient is as important as selecting the drug to be delivered. Medical specialists need to work on increasing the awareness among health care providers, regulatory agencies and insurers that dry powder inhalers are not interchangeable.

The error rate increased with age and with the severity of airway obstruction which is in line with previous studies [22, 30, 31]. The interaction of age, lung function, inhaler type and training in inhalational technique has implications that are not depicted adequately by mere calculation of inhaler-based error rates in the overall group. We therefore used the results from a mixed effects model analysis to estimate the risk of an ineffective inhalation in various clinical situations. According to this model, the risk of error is only 9.8% in the favourable case of an 18-year-old patient with normal lung function and previous instruction in the use of Turbuhaler. At the other end of the scale, a patient aged 80 with moderate or severe obstruction who has not received any instruction in its use has a risk of 83.2% of ineffective inhalation (fig. 3).

Inhaled steroids and long-acting bronchodilators improve the health-related quality of life of older patients with advanced COPD. These favourable effects have been shown in several carefully conducted randomised trials in which Discus, HandiHaler or Turbuhaler were used to deliver the medications [32–34]. It is to be assumed that patients who were incapable of handling these inhalers properly were excluded and that the participating patients received an optimal instruction on how to use their inhalers. These ideal conditions were not met in the patients investigated in the present study. Molimard et al. [15] pointed out that highly selective studies on which management guidelines are based do not represent patients in a typical outpatient setting. The favourable results of these studies should be extrapolated with caution to the real world, in which patients are often given a prescription for an inhaler without any instruction on inhalational technique other than the package insert. Borgström [35] postulated that COPD patients could use dry powder inhalers in an efficient way and that they would benefit from their use to the same extent as asthmatics do. This assumption was not confirmed by our study; the error rate in patients with severe COPD was disproportionately elevated. Figures 3 and 4 illustrate that a substantial proportion of older patients with severe COPD use Turbuhaler and Discus improperly even after instruction. Cognitive and psychomotor deficits occurring with the aging process as well as a COPD-specific cognitive impairment are likely to account for this finding [36].

Dry powder inhalers are a useful tool in the management of younger patients with normal lung function or mild airway obstruction provided that instruction in inhalational technique is given by medical personnel. In older patients the risk of ineffective inhalation remains high despite prior instruction. To ensure the efficacy of treatment, especially older patients with advanced COPD should be asked to demonstrate their inhalational technique at every health care encounter. If crucial handling errors cannot be eliminated by follow-up training, a metered-dose inhaler in combination with a large-volume spacer might be a valuable treatment alternative [37, 38].

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