Reduction in Patient Timing Errors Using A Breath-activated Metered Dose Inhaler*

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Delivery of aerosol medication to the lower respiratory tract by metered dose inhaler (MDI) is often limited by the patient's inability to properly coordinate activation of the device with inspiration. This study evaluated a new breath-activated MDI device, designed to minimize patient timing errors by sensing inspiratory flow and automatically activating to deliver aerosol medication. Twenty novice adult volunteers, previously naive to the technique of MDI use, and 20 patients currently using MDIs were tested in their ability to coordinate MDI usage. Simultaneous recording of respiratory events and device activation allowed analysis of timing errors. With a conventional MDI, a 31.0 percent incidence of errors was seen in the novice group and a 21.5 percent incidence of errors was seen in the experienced group. These compared with error rates using the breath-activated MDI of 6.5 percent and 5.0 percent in the two groups respectively (p=0.009, p=0.04). The breath-activated inhaler was preferred by 35 of 40 subjects. In conclusion, MDI technique timing errors were significantly less with this breath-activated MDI device in both novice and experienced subjects, and it was also preferred by both groups. ***(Chest 1994; 106:462-65)***

MDI=metered dose inhaler

Key words: aerosol therapy; asthma; metered-dose inhalers

Aerosol delivery of bronchodilator and anti-inflammatory medication to the lower respiratory tract by metered dose inhaler (MDI) is recognized as effective and safe therapy for obstructive airways disease.[1] Unfortunately, drug delivery by MDI is often compromised by the patient's inability to properly use the MDI device. Previous studies have shown that 14 to 96 percent of patients improperly use MDIs, depending on the population studied and number of MDI technique steps evaluated.[2-6] In studies that have examined the specific types of errors patients commit when using MDIs, improper coordination of device activation with inspiration is a major problem, with timing errors occurring in 15 to 65 percent of patients.[2-5,7]

Technique errors with MDIs have been shown to reduce the potential efficacy of bronchodilator medication administered from MDI.[8] In addition, technique errors may increase the incidence of oropharyngeal side effects from inhaled corticosteroids.[9] If the MDI is not fired until after inhalation has been completed, a large proportion of the dose may impact in the oropharynx.[10]

A new hand-held MDI device that is breath-activated (E-Z-V Inhalation Device, Allen and Hanburys) has recently been developed. It is designed to minimize patient timing errors by sensing inspiratory flow and automatically activating to deliver the aerosol medication. The present study examines timing errors in both naive and experienced subjects with regard to MDI use. Incidence of timing errors with conventional and the new breath-activated MDI are compared.

Methods

Conventional and breath-activated (E-Z-V Inhalation Device) metered dose inhalers were provided by Allen & Hanburys, Division of Glaxo Inc. The breath-activated inhalation device uses a mechanical system, triggered by the patient's inhalation, to actuate the MDI canister. Dose delivery is accomplished by the patient placing his or her lips around the mouthpiece of the device and inhaling. The device automatically releases the dose to the patient when inspiratory flow reaches 57.9±8.6 L/min (mean±SD).

Both conventional and breath-activated MDIs were similarly modified for timing analysis. A hole (0.125 inch diameter) was drilled into the side of each inhaler's plastic mouthpiece and plastic tubing (Tygon, Norton Performance Plastics) attached by means of a luer adapter (BF 3113, Becton Dickinson and Co). The tubing was then connected to a pressure transducer (Sectramed) and transducer amplifier (Model BPM-8802, Caldwell Systems), allowing measurement of changes in mouthpiece pressure occurring with inspiration. Mouthpiece pressure was continuously recorded on a dual channel flatbed recorder operating at 20 mm/s (Model BD 112, Kipp & Zonen). Stainless steel tubing (19 gauge, 0.375 inch long) was glued into the drug delivery port of each inhaler device. Polyethylene tubing (Intramedic PE-100, Becton Dickinson and Co) was attached and routed to a second pressure transducer for measurement of the pressure output occurring with device activation. This pressure was simultaneously recorded on an adjacent channel of the chart recorder, allowing comparison of timing of device activation with inspiration as per the method

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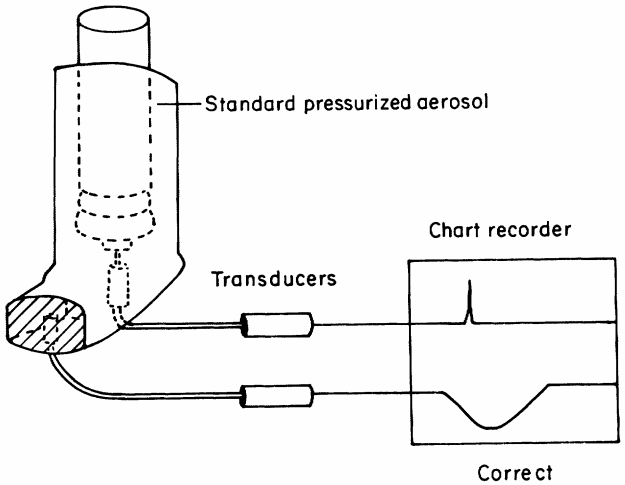

FIGURE 1. Schematic diagram of system recording respiratory events and canister activation (adapted from Coady et al[7]).

previously described by Coady et al (Fig 1).[7] Placebo canisters provided by Allen & Hanburys, containing propellant but no medication, were used in all aspects of this study. Canister output was carried via the polyethylene tubing to the pressure transducer, exposing subjects to neither medication nor propellant.

Clinical investigations were conducted using two groups of 20 volunteer subjects. The first 20 subjects were healthy normal adults who had never previously used MDIs and were naive with regard to the technique involved. The second group of 20 subjects consisted of individuals with previously diagnosed obstructive lung disease (asthma, emphysema, and chronic bronchitis), currently using a conventional MDI for therapy and self-judged to be proficient in MDI technique.

Subjects provided informed consent to a protocol approved by the Institutional Review Board of Virginia Mason Medical Center, Seattle. Subjects naive to MDI technique received standardized instruction in the use of both conventional and breath-activated devices, while those experienced with conventional MDIs were instructed only in use of the breath-activated device. Subjects were provided a set of printed instructions to read and were given brief demonstrations on use of the devices before testing. Patient technique errors were corrected before testing, with teaching intended to simulate the level of intensity that a patient might receive in a typical clinical setting.

Subjects then performed ten trials with each the conventional and breath-activated MDIs. The order of device testing was random, determined by a computer-generated code. Respiratory cycle and time of MDI activation were recorded simultaneously for analysis. Subsequent measurement of time intervals allowed comparison of timing of respiratory events with MDI activation. Each trial was categorized as being performed with either proper technique (activation of the canister during the first half of inspiration) or with a timing error. Two-tailed paired *t* testing was used for statistical analysis.

After completing the timing studies, subjects completed a questionnaire regarding the relative ease of use of the two devices and device preference.

RESULTS

Novice Subjects

Novice subjects ranged in age from 26 to 86 years, with a median age of 43 years. Nine men and 11 women were studied. Using the conventional MDI, a 31.0 ± 7.5 percent (mean $\pm$ SE) incidence of timing errors was seen, compared with a 6.5 ± 3.3 percent incidence of errors with the breath-activated MDI ($p=0.009$). Thirteen subjects had fewer timing errors with the breath-activated device, four with the conventional MDI, and three performed similarly with both devices.

Types of timing errors exhibited by novice subjects with the conventional MDI are listed in Table 1. Of the 200 trials, 62 were associated with a timing error. Among these, activation of the MDI before inspiration was most common, comprising 66 percent of errors. The MDI activation without inspiration and inspiration without MDI activation accounted for an additional 25 percent of errors. Four other types of timing errors comprised the remainder occurring with the conventional MDI.

Of the 200 trials performed by novice subjects with the breath-activated MDI, 13 were associated with a timing error. All were characterized as inspiration without device activation.

With regard to device preference, 85 percent of the novice subjects indicated that they would prefer to use the breath-activated MDI if they needed to use an MDI, 15 percent had no preference, and none chose the conventional MDI.

Experienced Subjects

Experienced subjects ranged in age from 18 to 76 years, with a median age of 40 years. Nine men and 11 women were studied. Using the conventional MDI, a 21.5 ± 7.1 percent incidence of timing errors was seen, compared with a 5.0 ± 2.5 percent incidence of errors with the breath-activated MDI ($p=0.04$). Eight subjects had fewer timing errors with the breath-activated device, three with the conventional MDI, and nine performed similarly with both devices.

Types of timing errors exhibited by experienced subjects with the conventional metered dose inhaler are also listed in Table 1. Of this group's 200 trials, 43 were associated with a timing error. Among these, activation of the MDI before inspiration was again most common, accounting for 65 percent of errors. Activation of the MDI late in inspiration, multiple MDI activations during a single inspiration, and inspiration without MDI activation comprised the remainder of the errors with the conventional MDI.

Of the 200 trials performed by the experienced group with the breath-activated MDI, 10 were associated with a timing error. Again, all were characterized as inspiration without device activation.

With regard to device preference among experienced MDI users, 90 percent would prefer to use the breath-activated MDI, 10 percent had no preference, and none chose the conventional MDI.

Table 1—*Types of Timing Errors in 200 Trials With Each Device in Novice and Experienced Subjects*

	Novice Subjects	Experienced Subjects
Conventional MDI		
MDI activation prior to inspiration	41	28
MDI activation without inspiration	11	
Inspiration without MDI activation	5	1
MDI activation late in inspiration	2	7
MDI activation after full inspiration	1	
MDI activation during expiration	1	
Multiple MDI activations during single inspiration	1	7
Total	62 (31.0%)	43 (21.5%)
Breath-Activated MDI		
Inspiration without MDI activation	13	10
Total	13 (6.5%)	10 (5.0%)

Discussion

Previous studies examining the technique of MDI use have found that the incidence of patient timing errors is significant.[2-5,7] Timing errors compromise the effectiveness of aerosol medication delivery. This is unfortunate, as administration of bronchodilator and anti-inflammatory medication from MDI is the basic form of asthma therapy in this country.[11] This investigation shows a significantly reduced incidence of timing errors with use of a new breath-activated MDI device in both novice and experienced subjects, providing the potential for significant improvement in treatment of patients with obstructive airways disease.

The incidence of timing errors varies widely in previously published studies, due both to use of varying criteria for proper technique and difference in populations studied. Activations of the MDI canister that occur before inspiration, after inspiration, without inspiration, or during exhalation are minimally effective. It has been clearly shown that aerosol bronchodilator effectiveness relates to the aerosol actually reaching the airways, not the fraction of a dose that impacts on the oral mucosa or is swallowed.[12] Such technique errors that result in excessive oral deposition can be easily eliminated through use of an effective breath-activated MDI device.

Relative effectiveness of MDI activations that occur at different phases of inspiration has also been examined. Activation of the MDI at lower lung volume (20 percent vital capacity) results in greater deposition of aerosol medication to the whole lung than activation at higher lung volume (50 percent or 80 percent vital capacity).[13] In this study, proper technique was defined as MDI canister activation during the first half of inspiration (see Methods section). Even with this relatively generous definition, 31 percent of trials by novice subjects and 21.5 percent of those by experienced subjects were associated with timing errors when using the conventional MDI. Some of these were from the device activation late in inspiration, but most errors with the conventional MDI were actually from activation prior to inspiration in both subject groups, an error which cannot occur with a breath-activated system.

Timing errors were not entirely eliminated with the breath-activated device. Of the 400 total trials performed with the breath-activated MDI, 23 (5.8 percent) were associated with an error. All of these were characterized as inspiration without device activation, apparently because the inspiratory flow rate during those trials was too slow or inadequate to activate the device's trigger mechanism. Inspiratory flow rate is an important determinant of lower respiratory tract aerosol deposition. Maximal bronchodilation or enhanced particle delivery to the lower respiratory tract or both have been shown to occur at inspiratory flow rates of 18 to 64 L/min, as compared with rates ranging from 80 to 192 L/min.[14-18] The breath-activated device tested in this study was designed to actuate at an inspiratory flow rate of about 58 L/min, within the optimal range for maximal aerosol delivery. While inspiratory flow was not measured in this study, this level is certainly achievable in most patients, as the mean peak inspiratory flow rate of random asthmatics has been shown to be 189 L/min (range 50 to 400 L/min).[19] In the rare instances where the breath-activated device was not activated in this study, it was immediately recognized by the subject because they did not hear the click associated with canister firing. Patients using this device would recognize the need to perform another maneuver to complete their medication dosing. This is in contrast to trials with the conventional MDI where subjects rarely realized that they had committed a timing error.

This breath-activated MDI device is additionally equipped with a manual override button that allows canister activation on demand. It is not inconceivable that a patient with neuromuscular weakness or extremely severe airflow obstruction might be unable to generate sufficient inspiratory flow to trigger the device automatically. The override button serves as a safety feature to allow manual canister activation in such instances, but does require the same coordination with inspiration as a conventional MDI. Another group that may have difficulty generating sufficient inspiratory flow is young children. It would be reasonable to withhold use of the device in chil-

dren until results of pediatric studies of the device are available, unless aerosol administration is being performed via manual device activation by the parent.

Timing errors using the conventional MDI were more frequent in novice subjects than the group experienced with MDI technique and use. Subjects in the experienced group were recruited from among patients of two general pulmonary practices and included patients with both asthma and chronic obstructive pulmonary disease. Familiarity with conventional MDIs and previous instruction likely contributed to the lower error rate. Similar results have been noted in other investigations, including one that reported nearly twice as many errors among experienced MDI users from a general internal medicine clinic as compared with those from a pulmonary medicine clinic.[5] The present study showed a significant reduction in timing errors with the breath-activated MDI device in novice and experienced patients alike, suggesting that both groups may benefit from the device.

Proper clinical instruction in MDI technique can be quite time consuming, requiring up to 28 min for initial instruction.[3] While instruction time was not actually measured in this study, the low incidence of timing errors seen with the breath-activated MDI device was achieved by asking patients to read a simple set of standard instructions, followed by a brief demonstration lasting less than 2 min.

A final advantage of this breath-activated MDI device is that it has the capability to accommodate a variety of brands of aerosol medication canisters, both bronchodilator and corticosteroid. The breath-activated device is acquired separately from medication, allowing physicians flexibility in prescribing. Cost savings that result from prescription of refill canisters rather than canisters plus standard MDI actuators are expected to equal approximately the cost of the breath-activated MDI device.

Future studies should examine the benefit that this device confers on control of airflow obstruction, as well as the effect of combination of the breath-activated MDI with spacer devices. The present study shows a clear reduction in timing errors as compared with a conventional MDI. It is recognized that some types of timing errors may be more detrimental to aerosol delivery than others, a hypothesis that could be examined through clinical efficacy studies. Spacer devices may confer additive benefits with regard to their effect on particle size and temperature, even without improving coordination in an individual with good MDI technique.

In summary, this study showed a significant reduction in MDI technique timing errors through use of a new breath-activated MDI device. This improvement was seen both in novice subjects and subjects experienced with MDI use. In addition, subjects in both groups overwhelmingly preferred the breath-activated device to a conventional MDI. This device has the potential to make a rapid and significant impact on MDI aerosol medication administration, especially in those patients with a tendency for timing errors with canister activation.

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