

Device mechanics and evaluation of inspiratory flow rate required of the beclomethasone dipropionate breath-actuated inhaler

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ABSTRACT

Background: Approximately 80% of patients with asthma and chronic obstructive pulmonary disease incorrectly use a metered-dose inhaler and, therefore, fail to obtain full benefit from their inhaler medication. Beclomethasone dipropionate (BDP) hydrofluoroalkane, an inhalation aerosol administered via a breath-actuated inhaler (BAI) has been designed to improve ease of use over press-and-breathe metered-dose inhalers by eliminating the need for hand-breath coordination.

Objective: To present the mechanics of the BAI device, assess the minimum reliable inspiratory flow rate required to trigger an actuation, and evaluate if intended users can safely and effectively use the BDP BAI according to the instructions for use (IFU).

Methods: Six random batches (three batches each of 40 µg and 80 µg) of 10 inhalers were evaluated for the minimum inspiratory flow rate required for actuation trigger. Each inhaler was tested for actuation at five flow rates: 12, 14, 16, 18, and 20 L/min. Simulated-use testing was conducted with 91 participants from six representative user groups in the United States to assess the use of a placebo-filled production-equivalent BDP BAI according to the IFU.

Results: Across the 40-µg batches, 83% of the devices actuated at 16 L/min and 100% actuated at 18 and 20 L/min. For the 80-µg batches, 67% and 100% actuated at 18 L/min and 20 L/min, respectively. All the participants demonstrated successful use of the BDP BAI during the study session. Isolated safety-critical errors with the potential for no-dose delivery were recorded for 15 participants but were considered unrelated to the design of the IFU.

Conclusion: The BDP BAI consistently triggered actuation at an airflow rate of 20 L/min and was successfully used based on guidance from the IFU only. This device provides an alternative for patients who find it difficult to use metered-dose inhaler devices correctly.

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According to the Global Initiative for Asthma guidelines,¹ the correct technique for press-and-breathe metered-dose inhaler (MDI) use is a critical

factor for effective asthma control. However, many patients do not appear to achieve complete benefit from their inhaled medication because only ~20% of patients with a history of asthma or chronic obstructive pulmonary disease use their inhaler correctly.^{2,3} Similar rates of inhaler misuse have been reported in MDI and dry powder inhalers (DPI).⁴ Improper use of MDIs has been associated with adverse outcomes, such as asthma exacerbations, an increase in frequency of emergency department visits, and irregular clinic follow-ups.^{5–8} For example, difficulties in coordinating actuation of an MDI with inhalation are common (a 90% prevalence has been shown in some studies^{9,10}) and have been associated with a greater risk of asthma exacerbation¹⁰ and a lower probability of achieving asthma control.^{5,8} The overall ease of use is one of the most important features of an asthma inhaler. Breath-actuated inhalers (BAI) improve ease of use over MDIs by eliminating the need for hand-breath coordination and potentially improve adherence and asthma control.¹¹

Beclomethasone dipropionate (BDP) hydrofluoroalkane, an inhalation aerosol administered *via* a BAI

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(QVAR[®] RediHaler[™]; Teva Respiratory, LLC, Frazer, PA),¹² was developed to help patients coordinate their inspiration with inhaler actuation. The BAI automatically delivers a metered dose of BDP when the patient inhales, without the need to press a canister or button to release the drug product, which eliminates both the need for priming and coordination of inhalation with actuation. The BDP BAI force-holding unit (FHU) has been designed to trigger with a flow rate ≤ 25 L/min.

The efficacy and safety of BDP BAI was reported in three phase III double-blind, randomized clinical trials in patients ages ≥ 12 years^{13,14} or 4–11 years who had persistent asthma.¹⁵ In two of these studies, the majority of the patients reported that the BDP BAI was “very easy” to use for the delivery of medication.^{13,15} The device is now approved in the United States for the maintenance treatment of asthma as prophylactic therapy in patients ages ≥ 4 years.¹² In the present study, we assessed the minimum reliable inspiratory flow rate required to trigger an actuation. We also conducted a simulated-use validation study to evaluate if intended users can safely and effectively use the BDP BAI according to the instructions for use (IFU) and if they can correct any use error to achieve competence.

METHODS

Device Mechanics

The BDP BAI uses a pneumatic system that combines breath-actuated technology with a primeless, fast-fill, fast-emptying metering valve that delivers a metered dose. This is recorded with a dose counter that displays the remaining doses, without the need to prime the device before use. The main components of the BDP BAI device are the following: the mouthpiece cover, which also works as an operating lever that prepares the device for the next metered dose when opened; the primeless valve, which provides primeless metering for the delivery of metered doses and contains the inhalation solution; the canister, which contains the pressurized inhalation solution; and the FHU, which provides sufficient energy to actuate the canister on inhalation (Fig. 1). The operating instructions for the patient describe the three main steps to operate the BDP BAI (Fig. 2).

The principal mode of operation of the BDP BAI is as follows. Before inhalation, the flap valve creates a vacuum seal with the opening of the diaphragm in the FHU to prevent the compression spring from actuating the canister. When air is drawn into the BDP BAI during inhalation, the flap valve is displaced, which breaks the vacuum seal with the diaphragm; and the compression spring is released, which forces the canister downward and results in the release of a metered dose by the primeless valve. Each actuation also causes the dose counter reading to decrease by one click.

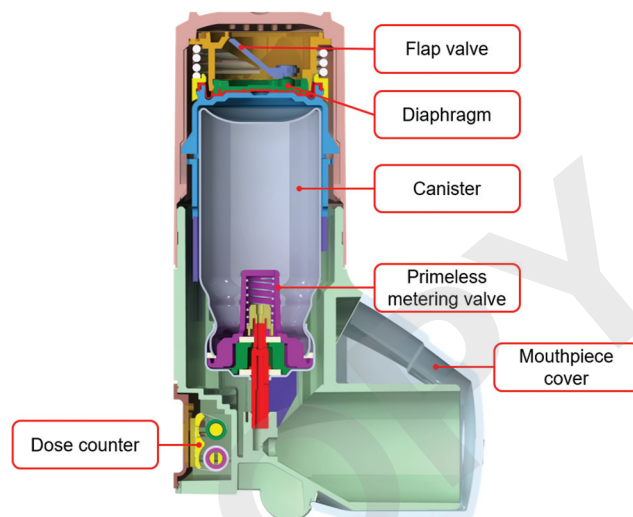


Figure 1. Cross-sectional view of the beclomethasone dipropionate (BDP) breath-actuated inhaler (BAI). The inhaler consists of three subassemblies: a main body assembly (green), a filled canister closed by a primeless fast-fill fast-empty metering valve (gray), and a force-holding unit (FHU) (brown).

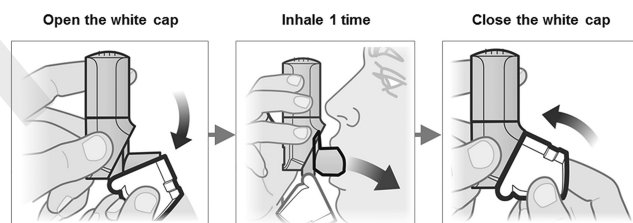


Figure 2. Instructions for patients for the use (IFU) of the beclomethasone dipropionate (BDP) breath-actuated inhaler (BAI): (1) Open the white cap (mouthpiece cover) and breathe out fully; never breathe out into the inhaler mouthpiece; (2) place the mouthpiece in your mouth, close your lips around it to form a good seal, inhale deeply to release the medicine, remove the inhaler from your mouth, hold your breath for 5–10 seconds, then breathe out slowly, away from the inhaler; (3) close the white cap after inhaling to prepare for the next inhalation. *If the patient has been instructed by their healthcare provider to take more than one inhalation per dose, then the white cap must be closed and steps 1–3 repeated.

When the mouthpiece cover is closed, air is expelled from the diaphragm components, the canister is prevented from being actuated, the dose counter components are reset to prepare for the next actuation, and the primeless valve is returned to the open position.

Objectives and End Points

The objectives of this study were to evaluate the minimum reliable inspiratory flow rate required to trigger an actuation of the BAI and to demonstrate that the BDP BAI, including the associated IFU and enhanced product labeling, can be used safely and effec-

tively by representative users, with no patterns of safety-critical use errors identified.

Determination of Minimum Inspiratory Flow Rate

Six batches of BDP BAIs were assessed during the study (three batches each of 40 μg and 80 μg inhalers). From each of these six random batches, 10 inhalers were evaluated for the minimum inspiratory flow rate required for actuation trigger. Each inhaler was tested for actuation by drawing air through the inhaler at five flow rates: 12, 14, 16, 18, and 20 L/min. The inhalers were weighed before and after each test to confirm that the inhaler had actuated; a 60-mg decrease in weight was the criterion to confirm that the inhaler had actuated.

Simulated-Use Validation Testing

Simulated-use testing was conducted with 91 participants from six representative user groups in two locations in the United States: 16 adults naive to MDI use, 15 adults experienced with MDI use, 15 adolescents naive to MDI use, 15 adolescents experienced with MDI use, 15 children naive to MDI use, and 15 children experienced with MDI use. This was a human factors study that used placebo, noninvasive inhaler devices, and, thus, no institutional review board approval was required. All the participants or their respective guardians or parents provided written informed consent before participation.

A worst-case realistic self-training approach was used; the only form of training was through the device IFU, without any guidance from the moderator. The participants were provided with an unused placebo-filled production-equivalent BDP BAI (individually packaged inside a cardboard carton with the IFU) and were instructed to demonstrate inhaler use as if they were going to use the inhaler for the first time. They were then asked to perform simulated inhalations according to a scenario whereby doses of medication were required to be administered. Individual in-depth interviews (~30 minutes in duration) were then conducted by experienced moderators and observed *via* a one-way mirror, to assess the safety and effectiveness of the BDP BAI and its associated IFU. Successful task performance was defined when the participants demonstrated competent inhaler use.

RESULTS

Minimum Inspiratory Flow Rate

Actuation of the BDP BAI at both dose strengths was triggered reliably by an airflow rate of 20 L/min. Across the 40- μg batches, 83% of the devices actuated at 16 L/min and 100% actuated at 18 and 20 L/min (Fig. 3A). One inhaler triggered actuation at 12 L/min but did not trigger again at <18 L/min. Among the

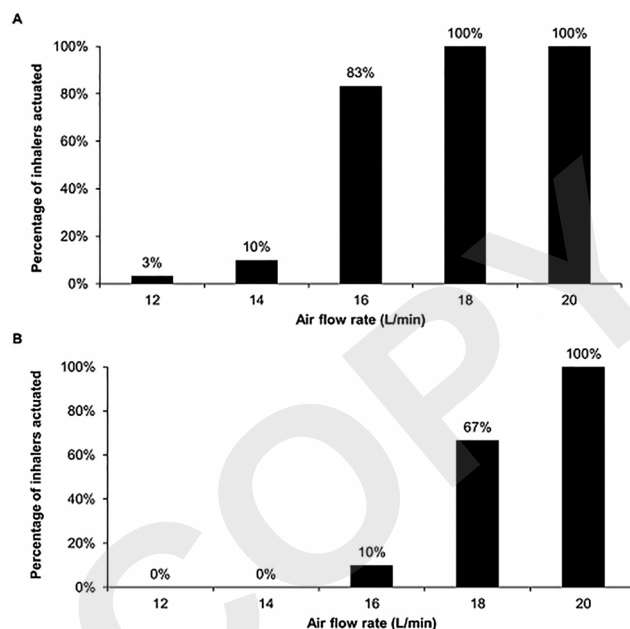


Figure 3. The percentage of inhalers ($N = 30$) triggered at different airflow rates for beclomethasone dipropionate (BDP) breath-actuated inhaler (BAI) (A) 40 μg and (B) 80 μg .

80- μg batches, 67% of the devices actuated at 18 L/min, whereas 100% actuated at 20 L/min (Fig. 3B).

Simulated-Use Validation Testing

All 91 participants used the BDP BAI at least twice and demonstrated successful use of the device during the study session. Nineteen participants committed isolated safety-critical use errors during the study. Of these, 15 participants recorded use errors during the first attempt, in which the use of the IFU was optional. A pattern of a noncritical use error (omitting to close the mouthpiece cover between inhalations) was observed for five participants, who corrected this error either unprompted or after being prompted to review the IFU. Use-related risk assessment identified this as a negligible or minor hazard severity.

IFU comprehension was generally high, with no evidence of participants misunderstanding critical statements that related to device storage, cleaning, or otherwise. Performance was generally associated with the attention level given to the IFU: if the participants engaged with the IFU, then they understood the critical elements of the procedure. Isolated safety-critical errors with the potential for no dose delivery were recorded for 15 participants during the study. The most frequent errors were in taking one inhalation instead of the prescribed two and failure to close the cap between inhalations, but these were not considered to be related to the design of the IFU. No pattern of safety-critical use errors, which may result in repeated failure to

deliver the inhalation medication to the lungs, was observed.

DISCUSSION

The BDP BAI offers an alternative inhalation medication delivery system that improves ease of use by eliminating the need for patients to coordinate their inhalation with actuation, which is a common problem associated with conventional MDIs.¹¹ The primeless valve in the BDP BAI further simplifies user requirements by removing the need for initial priming and repriming throughout the life of the device. Although the use of a BAI is dependent on a patient's inspiratory effort, a recent study indicated that children, adolescents, and adults with asthma have lower inspiratory flow rates, in the range of ~58 to 75 L/min, compared with healthy adults, who have an inspiratory rate of ~78 to 85 L/min when using a DPI (Turbuhaler®, AstraZeneca, Södertälje, Sweden or Spiromax®, Teva Pharmaceutical Industries, Petach Tikva, Israel).¹⁶ In the present study, we assessed the minimum reliable inspiratory flow rate required to trigger an actuation in the BAI. We also undertook a simulated-use validation study to investigate if patients can safely and effectively use the BDP BAI according to the IFU.

In the inspiratory flow rate study, the BDP BAI 40- μ g devices were typically triggered at an airflow rate of ≥ 16 L/min, with all inhalers triggering an actuation at 18 L/min. The BDP BAI 80- μ g devices were usually triggered at an airflow of ≥ 18 L/min. Random FHU batches were used during packing of these batches of BDP BAI; therefore, any variability observed in the results may be attributed to the variability observed in FHU batches. The simulated-use validation study demonstrated that a wide range of representative users were capable of using the BDP BAI safely and effectively. There was no evidence of flaws related to the design of the user interface because all the participants successfully used the BDP BAI during the study.

Key methodological limitations of the validation study were the following: (1) because placebo inhalers were used, the inhalation technique could not be fully assessed; (2) the participants had to fully engage in the role play because they had to perform two consecutive simulated inhalations; it, therefore, was anticipated that some participants experienced some confusion or forgot to repeat the use of the inhaler; and (3) cleaning and storing this device could only be assessed through discussion with the participants and IFU comprehension.

CONCLUSION

The BDP BAI consistently triggered actuation at an airflow rate of 20 L/min, which was within the 25 L/min airflow rate requirement used in product test-

ing for the device and much lower than the average inspiratory flow rate recorded for patients with asthma when using a DPI (58–75 L/min). Given that the BAI has negligible device resistance, unlike DPIs, a 20 L/min airflow rate would be achievable for these patients. We also demonstrated that this BAI was successfully used based on guidance from the IFU only. The device, therefore, offered potential benefits in terms of ease of use and provided an alternative for patients who found it difficult to use MDI devices correctly. As for all inhalers, a minimum level of training is required to achieve optimal competence with the device¹⁷ and the device technique should be checked and corrected at every opportunity.¹⁸

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