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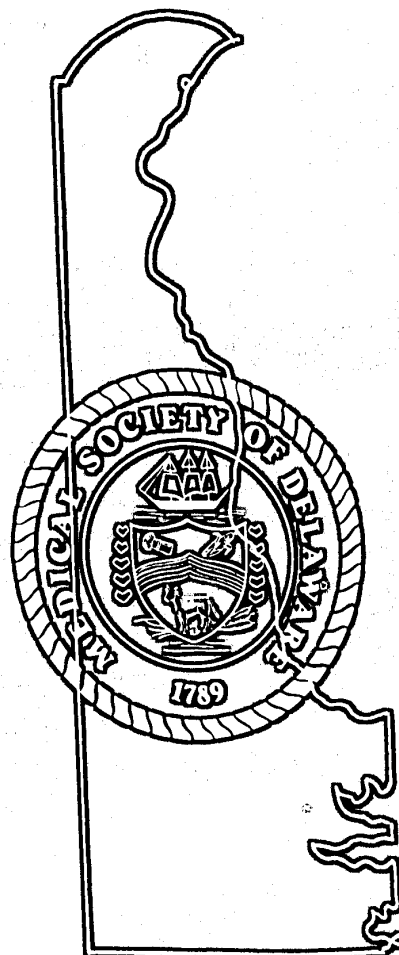
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SCIENTIFIC ARTICLE

When Should Your Asthmatic Patients Refill Their MDI Propelled with Chlorofluorocarbons?

Andrew G. Weinstein, M.D.

Abbreviations:

MDI = Metered-dose inhaler
CFCs = Chlorofluorocarbons
Vanceril 84 DS = Vanceril 84 mcg Double Strength
FDA = Food and Drug Administration

ABSTRACT

Background: The United States Food and Drug Administration has changed its policy regarding product labeling of asthma MDIs. All asthma MDIs propelled by CFCs should be discarded at the discard point labeled on the canister and box. This policy is in transition with inconsistent product information given to patients and physicians. Previously, patients had been educated to replace the canister by observing its floating pattern in water. Now FDA labeling asks users to count the number of actuations.

Objective: To compare the discard point of sample and prescription-size Serevent (6.5 g and 13 g) and Vanceril 84 DS (5.4 g and 12.2 g)

canisters to their floating pattern and total number of actuations in the canisters.

Design: Seven canisters each of Serevent 6.5 g and 13 g as well as Vanceril 84 DS 5.4 g and 12.2 g were shaken vigorously prior to actuation. One minute separated each actuation. The floating pattern was observed beginning at 80 percent of the discard point. This was repeated to the last actuation of the canister.

Results: The floating pattern (tilt point) indicative to replace the Serevent 6.5 g and 13 g canisters as well as Vanceril 84 DS 5.4 g canister occurred after the discard point was reached.

Conclusion: Floating patterns of the 6.5 g and 13 g Serevent inhaler as well as the 5.4 g Vanceril 84 DS do not assist the asthmatic patient in determining when to replace their canister. Because canisters have excess product and

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propellant beyond the labeled discard point, it may be possible for pharmaceutical companies to correlate the product's floating pattern to the drug concentration and particle size distribution up to and beyond the discard point. Through careful testing, floating patterns of MDIs may still be able to assist the asthmatic patient in determining when to discard the canister.

Very few asthma specialists, if any primary care physicians, are aware that all asthma metered-dose inhalers (MDI) propelled by CFCs must be discarded at the prescribed number of inhalations labeled on the canister and box, the "discard point." New FDA policy requires the manufacturer to place on the product information package insert that inhalations after the discard point are not assured for the correct amount of medication delivery. The FDA requires that drug product manufacturers submit data from sophisticated in vitro testing that assures that the labeled dose is delivered from the actuator throughout the labeled number of actuations for that product. These data are proprietary and are not available for public review. The FDA encourages sponsors to minimize the amount of "excess" formulation contained in the canister above that required to reliably deliver the labeled number of actuations. The FDA has always required that the product labeling state the number of actuations that the product is designed to deliver. Recently, the FDA has begun to require sponsors to also include in the product labeling statements that the amount of drug delivered per actuation after the labeled number of actuations have been delivered is unreliable and that the MDI should be discarded. The new statements in the labeling also instruct patients to keep track of the number of actuations used as this is the only reliable method, absent a counter mechanism on the MDI, for determining when the MDI should be replaced.

"Newer" drugs, such as Vanceril 84 DS and Combivent (Boehringer Ingelheim), as well as "older" drugs such as Azmacort (Rhone-Polenc Rorer) and Atrovent (Boehringer Ingelheim) had

sufficient data to be awarded new labeling for both patient and physician package information inserts. Medications manufactured by Glaxo-Wellcome (Ventolin, Beclovent, Serevent, and Flovent), Fisons (Intal, Tilade), Schering (Vanceril), and Zenith (albuterol) have discard point labeling in the patient package information insert, but not in the physician insert. Once these companies have fulfilled the necessary requirements, information regarding the discard point will appear on the physician's product information insert. Currently, Schering's Proventil, Warrick's Albuterol, Boehringer Ingelheim's Alupent, 3M Pharmaceutical's Maxair and Forest Pharmaceuticals' Aerobid and Aerobid M do not have discard point labeling in either patient or physician package information inserts. Despite the fact that many asthma MDIs do not have discard language for physicians, officials at the FDA acknowledge that all asthma canisters propelled by CFCs should be discarded after the patient has reached the specified number of inhalations on the canister or on the box.

A recent report by Wolf and Cochran suggests that the floating patterns of prescription-size MDIs can be correlated to the discard point³. If this is true, then asthmatic patients need not rely solely on counting the number of actuations inhaled before replacing the canister. The purpose of this brief report was to observe the floating pattern of both sample and prescription-size Serevent and Vanceril 84 mcg DS (Vanceril 84 mcg DS was not evaluated by Wolf and Cochran) and relate these findings to the discard point and the number of actuations in the canisters.

METHOD

Seven canisters were obtained for each of the sample size Serevent 6.5 g and Vanceril 84 DS 5.4 g MDIs from company representatives. Seven canisters were obtained for each of the prescription size Serevent 13 g and Vanceril 84 DS 12.2 g MDIs from a community pharmacy. Each MDI was discharged at room temperature, 68 de-

degrees Fahrenheit, humidity 35 percent with the valve down. Each canister was shaken vigorously before actuation and one minute separated subsequent shaking and actuation. Test floating began when the MDI had been actuated to 80 percent of the discard point.

Canisters were placed in a container of water 68-70 degrees Fahrenheit and the floating pattern (valve down) was observed. A canister was considered to be "tilted" when it no longer floated at 90 degrees to the water surface.

RESULTS

The discard point, the mean number of actuations to the tilt point, the mean number for the last actuation from the MDI and the mean percent of actuations after the discard point for sample and prescription-size Serevent and Vanceril 84 DS MDIs are presented in Table 1. Vanceril 84 DS 12.2 g tilt test correlates closely with discard point. The tilt point of both Serevent MDIs and Vanceril 84 DS 5.4 g occur after their discard point. The discard point of the sample-size of both Serevent 6.5 g and Vanceril 84 DS 5.4 g comes with more than 40 percent of the drug remaining in the canister. There is 23 percent of the Serevent 13 g and 27 percent of the Vanceril 84 DS 12.2 g remaining in the canister when it

should be discarded per FDA recommended guidelines.

DISCUSSION

On the surface, metered-dose inhalers are very simple devices; however, in actuality they are one of the most complex dosage forms available to patients for home use. A large number of complex factors including propellant vapor pressure, physical and chemical interactions between the active drug substance, propellants and inactive ingredients, valve performance, ambient temperature and humidity, adequacy of shaking, time interval between actuations, etc. influence the performance of these devices.⁴ These and other factors that may have an impact on the performance of MDIs require careful attention during the manufacturing process and require rigorous quality control testing to assure that patients receive a device that performs reliably when used under the conditions described in the product labeling. This is the reason for discard point labeling.

The results in this study confirm some of the general findings of Wolf and Cochran who examined the floating patterns of 13 common sample-size and 11 common prescription-size MDIs including Serevent.³ Vanceril 84 DS was

Table 1.

Product	Weight	Lot Number	Number Tested	Discard Point	Positive Tilt Test # Actuations Mean (Range)	Last Actuation Mean (Range)	Percent of Actuations Remaining After Discard Point
Serevent Sample-size	6.5 g	7ZP0081 7ZP0272	4 3	60	90 (88-92)	103 (99-104)	42%
Serevent Prescription-size	13 g	7ZP0914 7ZP1429	4 3	120	133 (132-135)	155 (152-157)	23%
Vanceril 84 mcg Double Strength Sample-size	5.4 g	7DMT 108	7	40	61 (59-62)	74 (71-76)	46%
Vanceril 84 mcg Double Strength Prescription-size	12.2 g	7DMT 601 7DMT 609	4 3	120	120 (118-122)	165 (163-168)	27%

not tested in that study. Wolf and Cochran found that six of the 13 sample-size MDIs had exceeded the discard point when they observed a "tilt" in the floating pattern. In their study, three of the sample-size Serevent 6.5 g canisters tested "tilted" when the discard point was exceeded by 25 percent. In this study, the seven sample-size Serevent 6.5 g and seven Vanceril 84 DS 5.4 g MDIs tilted when the discard point was exceeded by 50 percent. Our findings would support Wolf and Cochran's generalization that the tilt in the floating patterns of sample-size MDIs will occur after the discard point has been reached and would not assist the asthmatic patient in determining when to replace the MDI.

Our study of the prescription-size Vanceril 84 DS 12.2 g and Serevent 13 g only partially supported Wolf and Cochran's generalization that the floating pattern of all prescription-size MDIs can predict when to discard the inhaler. The investigation found that all 11 of the prescription-size MDIs tested, including Serevent 13 g, tilted prior to reaching the discard point. We found this to be the case with Vanceril 84 DS. The seven 12.2 g canisters we tested had a mean tilt point at 120 actuations, which is 100 percent of the discard point. However, we were unable to reproduce Wolf and Cochran's tilt point of the Serevent 13 g canister, which was 92 percent of the discard point. The seven tested Serevent 13 g MDIs tilted at a mean 110 percent past the discard point. The variance in findings between these two Serevent 13 g prescription-size MDI studies most likely reflects a difference in the methodology of testing. Wolf and Cochran had vigorously shaken the inhalers between each actuation without waiting, and test floated every five actuations. In our study, each canister was shaken vigorously before each actuation with at least one minute separating each actuation. Float testing began at 80 percent of the discard point. The difference in methodology yielded a greater number of actuations to the tilt point for both 6.5 g (75 vs 90) and 13 g (110 vs 133) MDIs. We examined only two asthma MDI products. A more comprehensive examination of other

prescription-size MDIs is required to see if they would also fall outside Wolf and Cochran's second generalization when tested with a one minute lapse between each actuation.

A fundamental design issue for all MDIs is a requirement that an excess of the propellant and drug formulation be placed in the MDI canister at the time of manufacturing to assure reliable delivery of the labeled dose from the actuator throughout the labeled number of actuations stated in the product labeling.⁵ This means that the MDI canister will not be empty of propellant and drug formulation when the labeled number of actuations have been delivered to the patient. Unfortunately, the dose delivered from the MDI beyond the labeled number of actuations is highly variable and the tail off pattern for each MDI product may differ significantly from the pattern of other MDI products.⁴ This fact is related to the fundamental design differences between various MDI products. Several drug information specialists, who were not permitted to provide precise information about their company's MDI products, estimated that most MDIs contain at least ten percent excess propellant and drug formulation in their canisters. One company, which requested anonymity, shared on file data in which their inhaled corticosteroid MDI gives consistent dosing of product up to 20 percent beyond the discard point. It is possible that the tilt point of Serevent 13 g (133 actuations) may fall within the range of the ten percent in excess of the labeled discard point (120 actuations) in this prescription-size MDI. Access to these pharmacologic bioavailability data on file may yet validate test floating as a tool for determining when to discard the MDI canister.

The float test is a commonly used, but overly simplistic and poorly validated method to determine when a MDI should be discarded.¹ Both this report and that of Wolf and Cochran are flawed in the methodology used to compare the floating patterns of MDIs to the labeled number of actuations. A critical aspect of MDI performance testing is missing in both papers, namely

quantitative and rigorously validated tests for the amount of drug substance delivered from the actuator and the particle size distribution of the delivered drug substance for each actuation up to and beyond the labeled number of actuations for the product. Without this fundamental information, a valid conclusion cannot be reached regarding the accuracy of the tilt point in determining when a MDI should be discarded. Furthermore, floating a MDI canister in water may damage the canister by allowing water ingress which can adversely impact the performance of the MDI. In fact, the Vanceril 84 mcg product tested in this study is packaged in a moisture protective pouch to guard against atmospheric humidity. Therefore, the float test is not only unreliable as an indicator of when a MDI should be discarded, it may also adversely affect the performance of the MDI and result in unreliable dosing even though the MDI has not yet reached the labeled number of actuations.

We would agree with Wolf and Cochran that part of the FDA's rigorous control testing to assure that patients receive a device that performs reliably should include float testing with diagrams indicating the remaining amount of formulation in the canister. A carefully validated float test, supported by a quantitative measure of drug concentration and particle size, would be a superior method to counting each actuation, as the asthmatic patient determines when to discard their MDI.

Electronic counting devices have been developed. The Doser®, manufactured by New Med in Waltham MA, is one such device. Counting devices attach to the MDI and provide a read out of the number of actuations used. These devices are commercially available; however each counter can track only one MDI at a time. With the advance and application of microprocessor technology, MDIs of the future may be capable of both counting the number of actuations as well as monitoring compliance with treatment by recording the date and time of each actuation. Currently, there is a device available (SmartMist

by Aradigm - Hayward CA) which can monitor compliance, measure peak flow value and optimize drug delivery; however, this device does not track the number of actuations.

The pharmaceutical industry is making plans to phase out inhalers containing CFCs because of their harmful effect on the earth's ozone layer. Dry powder propellants for individuals with asthma have been available in other countries and are now available in the United States. Pulmicort (budesonide - Astra), an inhaled corticosteroid, and Serevent Diskus (salmeterol - Glaxo-Wellcome), a long-acting bronchodilator, have markers or dose counters that indicate when the inhaler should be replaced. In the future, questions regarding when to discard the asthma inhaler may be an issue of the past.

REFERENCES

1. Williams DJ, Williams AC, and Kruchek DGB. Problems in assessing contents of meter-dose inhalers. *Br Med J.* 1993; 307:771-772.
2. 62 Federal Register 10242 (March 6, 1997).
3. Wolf BL and Cochran KR. Floating patterns of metered-dose inhalers. *J Asthma.* 1997; 34:433-436.
4. Shultz RK. Drug delivery characteristics of metered-dose inhalers. *J Allergy Clin Immunol.* 1995; 96:284-287.
5. Cyr TD, Graham SJ, Li KYR, and Lovering EG. Low first-spray drug content in albuterol metered-dose inhalers. *Pharm Res.* 1991; 8:658-660.

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