

Effect of formulation parameters on hydrofluoroalkane-beclomethasone dipropionate drug deposition in humans

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Chlorofluorocarbon metered dose inhalers (MDIs) and dry powder inhalers currently deliver drug that deposits primarily in the oropharynx and secondarily in the large central airways. Chlorofluorocarbon-beclomethasone dipropionate (CFC-BDP) MDIs deliver more than 90% of the drug in the oropharynx and less than 10% in the lungs. The elimination of chlorofluorocarbons from MDIs provided the opportunity to more optimally target corticosteroids directly to all inflammatory sites. Hydrofluoroalkane-BDP (HFA-BDP) MDIs (QVAR™) deliver 50% to 60% of the drug to the lungs with approximately 30% delivered to the mouth. Additionally, the amount of drug delivered to the lungs is distributed throughout the large, intermediate, and small airways. Radiolabeled deposition studies have shown that the HFA-BDP MDI is a "forgiving" aerosol in that even the extreme discoordinated use of the press and breathe MDI still resulted in more than 30% lung deposition. The breath-actuated Autohaler inhaler provided the same lung deposition as an optimally used press and breathe MDI. The dose delivered from either the press and breathe HFA-BDP MDI or the Autohaler was consistent across a wide range of inspiratory flows (eg, flows of 26-137 L/min). Clinical studies have shown that the improvements in lung deposition of HFA-BDP result in equivalent efficacy at approximately one half of the total daily dose compared with current CFC-BDP products. (*J Allergy Clin Immunol* 1999;104:S250-2.)

Key words: Beclomethasone, lung deposition

Chlorofluorocarbon production was eliminated by the 150 signatory countries of the Montreal Protocol.¹ Complete phase-out proposals for chlorofluorocarbon products will occur when technically and economically feasible alternatives exist. The United States Food and Drug Administration has proposed that when 3 suitable substitutions in a therapeutic category are available (eg, β -agonists, steroids), chlorofluorocarbon products in that class will be eliminated from the market. Eliminations may also occur on a molecule-by-molecule basis.² Hydrofluoroalkane-134a is an alternative for the chlorofluorocarbons that does not contain chlorine and therefore does not destroy ozone. The pharmaceutical consortium (International Pharmaceutical Aerosol Consortium for Toxicity Testing) showed that hydrofluoroalkane-134a is safe for use as an MDI propellant.³

Abbreviations used

CFC-BDP:	Chlorofluorocarbon-beclomethasone dipropionate
HFA-BDP:	Hydrofluoroalkane-beclomethasone dipropionate
MDI:	Metered dose inhaler

TABLE I. Deposition of radiolabeled HFA-BDP versus CFC-BDP

	Lungs (%)	Oropharynx (%)	Exhaled (%)
Subjects			
HFA-BDP (n = 6)	55 $\pm$ 12*	29 $\pm$ 13	14 $\pm$ 4
CFC-BDP (n = 6)	4 $\pm$ 3	94 $\pm$ 4	0 $\pm$ 0
Patients with asthma			
HFA-BDP (n = 16)	56 $\pm$ 9	33 $\pm$ 9	9 $\pm$ 4

*Values represent mean $\pm$ SD of the ex-actuator dose.

Corticosteroid inhalers are increasingly recommended to treat asthma and other lung diseases because they treat the underlying causes of asthma.⁴ However, chlorofluorocarbon steroids will eventually be eliminated. Ironically, this elimination has provided the opportunity to improve their performance, specifically in the area of delivering more drug to the lungs and less drug to the oropharynx. Chlorofluorocarbon and dry powder steroid formulations deposit from 5% to 30% in the lungs and the remainder of the drug in the oropharynx.⁵ Less drug in the lungs reduces therapeutic benefit, and drug in the mouth can cause local side-effects such as candidiasis and thrush. Drug deposited orally can add to systemic exposure and consequently effect the hypothalamus-pituitary-adrenal (HPA) axis, bone metabolism, and growth.⁶ Asthma has been shown to be an inflammatory disease of the peripheral airways and of the large central airways,⁷ yet very little chlorofluorocarbon steroid penetrates to peripheral airways because of the relatively large size of the emitted particles from the inhalers.⁸ With these factors in mind, the new hydrofluoroalkane-beclomethasone dipropionate (HFA-BDP; QVAR) inhaler was designed to increase lung deposition and decrease oropharyngeal deposition, without the use of add-on spacers.

A powerful tool for determining the site of aerosol drug deposition involves radiolabeling the drug with

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TABLE II. Deposition as a function of HFA-BDP inhaler coordination

	Time to actuate* (sec)	Lung (%)	Oropharynx (%)	Exhaled (%)	Relative peripheral† (%)
Autohaler	0.2	56‡	29	14	29
P&B on-time	0.4	58	26	13	26
P&B early	-0.5	34	57	8	24
P&B late	2.5	32	24	43	31

P&B, Press and breathe.

*Values are relative to the start of a 3-second inspiration.

†Lung regions were divided into central, intermediate, and peripheral regions.

‡Numbers represent the mean of the ex-actuator dose.

technetium-99m. A major concern in the use of this tool has been the consistency of the radiolabeling procedure and the proper validation that the radiolabel is present on all representative particle sizes of drugs. The validation conducted on HFA-BDP and chlorofluorocarbon-BDP (CFC-BDP; Beclovent™) showed that there was good association of radiolabel and drug for each study described in this paper.⁸

RESULTS

The average particle size of HFA-BDP is 1.1 μm (mass median aerodynamic diameter) compared with 3.5 μm for CFC-BDP. The average spray force for HFA-BDP is 3 times less than chlorofluorocarbon-steroids (ie, approximately 35 milliNewton (mN) for HFA-BDP versus approximately 100 mN for CFC-BDP, chlorofluorocarbon-fluticasone, and hydrofluoroalkane-fluticasone). The duration of spray is longer for HFA-BDP versus the CFC-BDP (ie, approximately 250 msec for HFA-BDP versus 150 msec for CFC-BDP). The temperature of the spray is warmer for HFA-BDP than for the chlorofluorocarbon-steroids (ie, approximately +5°C for HFA-BDP versus -20°C for chlorofluorocarbon-steroids). A smaller particle size and a softer, warmer, slightly longer spray resulted in more lung deposition and less mouth deposition for HFA-BDP compared with CFC-BDP (Table I). Lung scans were performed on each patient with the use of xenon-133 gas to determine the maximum relative distribution within the lungs. The lungs were divided into regions, and the distribution of HFA-BDP was compared with the distribution of xenon-133 gas. The relative distribution of HFA-BDP was nearly identical to that of xenon-133, showing that the particles of HFA-BDP were nearly ideally dispersed throughout the lungs.

It has been estimated that at least 50% of patients exhibit poor inhaler technique. Most of the poor technique involves actuating the inhaler before the beginning of the inspiration cycle or too late in the inspiration cycle. The smaller particle size and longer duration spray of HFA-BDP MDIs resulted in patients receiving more than 30% lung deposition even under the severe discoordination of actuating before inhaling and as late as 2.5 seconds after the start of inspiration (Table II). These same patients received approximately 58% lung deposition if they actuated the HFA-BDP inhaler on time. Patients also

received approximately 56% lung deposition if they used a breath-actuated inhaler (QVAR™ Autohaler). In addition, the relative distribution of HFA-BDP remained the same whether the patient was coordinated or discoordinated (eg, peripheral lung deposition was always approximately 27% of the total lung dose; Table II).

The HFA-BDP inhaler was also evaluated in healthy subjects and patients with asthma over a wide range of flows, specifically between 26 and 137 lpm inspiratory flow. The average lung deposition was approximately 58% and did not change over the inspiratory flow rate range.

Clinical efficacy and pharmacokinetic studies have confirmed lung deposition predictions. A clinical dose response study comparing HFA-BDP and CFC-BDP showed that HFA-BDP had equivalent efficacy at 2.6-fold less dose than CFC-BDP when FEV₁ values were used and 3.2-fold less dose than CFC-BDP when FEF₂₅₋₇₅ values were used as the outcome parameters.

CONCLUSIONS

The elimination of chlorofluorocarbons from MDI provided the opportunity to improve the dosing characteristics of steroid inhalers. The new HFA-BDP MDI QVAR reverses the pattern of deposition of the old chlorofluorocarbon-steroid products because the HFA-BDP inhaler delivers approximately 60% of the drug to the lungs compared with less than 10% for CFC-BDP MDIs. Approximately 30% of HFA-BDP is deposited in the mouth compared with more than 90% mouth deposition for CFC-BDP MDIs. In addition, the HFA-BDP MDI deposits the drug throughout the lung's large and small airways compared with CFC-BDP lung deposition, which is primarily in the large central airways. The improved dosing characteristics have also resulted in a more 'forgiving' aerosol because, with even discoordinated use of the inhaler, more than 30% lung deposition occurred, still maintaining an even distribution within the lungs. The lung deposition is also unaffected by the patient's inspiratory flow rate across a wide range.

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