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Hydrofluoroalkane as a propellant for pressurized metered-dose inhalers: history, pulmonary deposition, pharmacokinetics, efficacy and safety

Cássio C. Ibiapina,[1] Álvaro A. Cruz,[2] Paulo A. M. Camargos[3]

Abstract

Objective: To review the literature about hydrofluoroalkane as a propellent of pressurized metered-dose inhalers containing anti-asthma drugs.

Sources of data: Bibliographic search in electronic databases (MEDLINE, MDConsult, HighWire, Medscape and LILACS) and direct search referring to the past 15 years, using the key words hydrofluoroalkane, asthma and childhood were carried out.

Summary of the findings: 43 original articles on the replacement of clorofluorcarbon by hydrofluoralkane were selected. Hydrofluoralkane showed to be a safe propellent, with pulmonary deposition ranging from 50 to 60%, and to have significant efficacy, when compared with placebo ($p \leq 0.003$) in controlled clinical trials. Most works using hydrofluoralkane included beclomethasone diproprionate. Approximate annual cost of a treatment with beclomethasone diproprionate/hydrofluoralkane was lower than with beclomethasone diproprionate/clorofluorcarbon. Some studies assessed salbutamol, fluticasone, flunisolide and the association fluticasone-salmeterol, with hydrofluoralkane as propellent in pressurized metered-dose inhalers.

Conclusions: Efficacy and safety of hydrofluoralkane as propellent of bronchodilators and inhaled corticosteroids in adults was evidenced, as well as, in general, there was a better pulmonary deposition of particles. However, literature data on the use of hydrofluoralkane in the paediatric age group are still scarce and further studies with children and adolescents would be of great importance.

J Pediatr (Rio J). 2004;80(6):441-6: Asthma, hydrofluoralkane, treatment, aerosol.

Introduction

Inhalation, used ever since medicine exists, became very popular in the late 19th century. At that time, medications were put in boiling water so that patients could inhale their vapor.[1]

In the specialized 20th-century literature, the first reports on aerosol therapy for the treatment of asthma data back to the 1950s, when pressurized metered-dose inhalers (pMDI) were introduced, representing an undeniable improvement in the treatment of respiratory disorders. At present time, it is widely known that the prescription of pMDI exceeds 500 million units a year on a worldwide basis, and that their use has been increasing decade after decade.[2]

Inhaled corticosteroids are regarded as first-line treatment, recommended in every consensus for the management of persistent asthma, and often are delivered via a pMDI. Chlorofluorocarbon (CFC) is the most widely used propellant in pMDI; it is inexpensive, safe and efficient, but its use has been universally restricted due to its deleterious effects on the ozone layer.[3]

The first evidence that CFC and other chlorine-containing products contribute to ozone layer depletion was gathered in the 1970s.[4] Because of these substances, the ultraviolet radiation that reaches the Earth's surface is increased, producing severe adverse effects on man, such as skin cancer, cataract and lower immunological resistance. Birds, sea life, plastic and other materials also are affected.[5]

1. Doctoral student, Graduate Program in Pediatrics, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil.
2. Coordinator, Center of Respiratory Diseases, School of Medicine, Universidade Federal da Bahia (UFBA), Salvador, BA, Brazil.
3. Full professor, Department of Pediatrics, School of Medicine and Head of the Pediatric Pulmonology Unit, Hospital das Clínicas, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil.

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The hole in the ozone layer formed over Antarctica, observed in the early 1980s, has been expanding every year. Recent studies have estimated its size as being as large as 23 million square meters, which corresponds to nearly three times the size of Brazil.

An international agreement, known as the Montreal Protocol,[5] which aimed to control the production and consumption of substances that can cause ozone depletion, was signed in September1987. The agreement established a 50% reduction in CFC production per year until 1998. In 1990, due to the ample evidence regarding CFC and ozone layer depletion, an amendment banned the manufacture of CFC fire extinguishers from the year 2000 onwards. In 1992, as ozone layer depletion worsened, CFC production was prohibited until late 1995, being only allowed in medications until 2005. Thus, pMDI are the only exception to CFC production and consumption, since they were considered essential to the treatment of asthma.[6]

In 1995, two safe and efficient propellants – hydrofluoroalkane 134a (HFA 134 a) and hydrofluoroalkane 227ea (HFA 227ea) – were acknowledged by the European Union.[6] In 1996, the Food and Drug Administration (FDA) approved the use of HFA 134a in inhalers.[7]

HFA does not affect the ozone layer, but it exerts a significant effect on global warming, as it is one of the six greenhouse effect gases.[8]

In 1997, the United Nations Framework Convention on Climate Change – the Kyoto Protocol – approved the resolutions of the Earth Summit that took place in Rio in 1992. The Kyoto protocol expanded those resolutions, placing heavy emphasis on the emission of greenhouse effect gases in the USA. Of note, although the Kyoto Protocol was signed by 55 countries, including industrialized ones, it was not ratified by the United States, and therefore it does not have the force of law in its territory.[4,6]

The Kyoto Protocol devised mechanisms for the management of climate changes, especially with regard to the reduction in the production of gases that can cause global warming. The six greenhouse effect gases (carbon dioxide, methane, nitric oxide, hydrofluoroalkane, perfluorocarbon and sulfur hexafluoride) were gathered into a single group. This approach gives countries more flexibility to choose the percentage of reduction for each gas, so that they can achieve the total reduction goal established by the protocol.[6]

HFA, along with sulfur hexafluoride and perfluorocarbons, have a large heat-generating capacity. However, as they account for only 1.8% of the greenhouse effect gases emitted in the USA, their contribution to global warming is negligible.[6,7]

The use of HFA in pMDI is a medical option with enormous value to health; therefore, every nation should guarantee its availability to the population. Given this CFC/HFA transition period, the aim of this review is to discuss the aspects related to the pharmacokinetics, efficacy, safety and use of HFA in the treatment of asthmatic patients.

Deposition of beclomethasone dipropionate and CFC- and HFA-containing pMDI

The CFC/HFA transition resulted in the development of aerosol technology. Beclomethasone dipropionate (BDP), the oldest type of inhaled corticosteroid, has been used in asthma treatment for over two decades. The combination of BDP and HFA 134a results in an aerosol with much smaller particles than those produced by CFC inhalers. Mathematical models that relate particle size with the site of deposition in the respiratory tract and experimental upper airway models demonstrate that the particles produced by HFA have an enhanced small-airway deposition, whereas those particles produced by CFC tend to have a more proximal deposition, also in the oropharynx.[9-13]

CFC-containing pMDI and powder inhalers release the drug, which is first deposited in the oropharynx and then in the large airways. Of the BDP applied via a CFC-containing pMDI, over 90% of the drug is deposited in the oropharynx and less than 10% in the lungs. If applied via an HFA-containing inhaler, the rate of lung deposition may reach 60%, whereas approximately 30% is deposited in the oropharynx.[10] The average size of the HFA-BDP particle is 1.1 micra, and that of CFC-BDP, 3.5 micra. The necessary manual force to press down on the HFA-BDP spray is three times smaller than that which is required for CFC sprays. The HFA-BDP spray duration is longer (250 milliseconds) than that of the CFC-BDP (150 milliseconds). Plume temperature is higher in HFA-BDP (5 °C) than in CFC-BDP (-20 ºC), which reduces the undesirable cold-freon effect. The physical characteristics of the jet and particles of HFA-BDP are responsible for enhanced lung deposition and smaller deposition in the oropharynx.[12]

It should be underscored that less than 50% of the patients use the inhalation technique properly, by pressing down on the inhaler before starting to breathe in or due to the late delivery of medication in the inspiratory cycle. The smaller particle size and the longer duration of the HFA-BDP spray allow for enhanced deposition in the airways even in those patients with serious coordination problems.[10]

In a clinical dose-response trial, Bogston et al. showed that the efficiency of HFA-BDP is equivalent to a dose 2.6 times higher of CFC-BDP when the forced expiratory volume in one second (FEV_1) was assessed, and to a dose of 3.2 times smaller of HFA-BDP when the maximal midexpiratory flow rate was analyzed (FEF_{25-75}).[14]

HFA as a propellant for other drugs: salbutamol, fluticasone, flunisolide, combined with salmeterol and non-extrafine formulation

In the specialized literature, several studies have shown that in salbutamol-containing formulations, the particle sizes in CFC-, HFA-containing pMDI, and in powder inhalers were equivalent. We may infer that the percentage of lung deposition and therefore the clinical effects are similar in these three formulations. These studies also have shown that there is no significant difference in the improvement of FEV_1.[14-23]

Two studies assessed the efficacy of fluticasone-HFA. Fowler et al., in a randomized double-blind study that

evaluated 18 adult patients for six weeks, compared the efficiency of fluticasone-HFA versus fluticasone-CFC. A group of nine patients used 500 µg of fluticasone-HFA, and another group inhaled 1,000 µg of fluticasone-CFC, but no statistically significant difference was observed ($p = 0.21$) between the groups.[24] Langley et al. published a study in which they demonstrated an equivalent decrease in airway hyperresponsiveness after the administration of equal doses of fluticasone-HFA and fluticasone via the Diskhaler® system.[25]

In Brazil, salbutamol and fluticasone, both in separate formulations, and the combination of fluticasone and salmeterol have been the commercially available options until now. However, other drugs containing HFA are expected to be marketed in Brazil in the future, given the imminent CFC phaseout deadline.

Hauber et al. published a clinical trial involving 12 adult asthmatic patients showing the efficacy of flunisolide-HFA.[26] The authors observed suppression of eosinophil inflammation of peripheral and central airways by analyzing transbronchial and endobronchial biopsies, before and after the use of flunisolide-HFA. They found significant improvement in pulmonary function ($p = 0.012$), decrease in the number of eosinophils, with a reduction from 51.5±5 to 14.6±3.2 cells/mm^2, interleukin-5 and eotaxin in central and peripheral airways with a reduction from 37.3±6.2 to 16.7±3.2/mm^2 and from 38.8±5.5 to 22.3±3.1/mm^2, respectively. In this study, the researchers show the possible role of smaller particles of HFA, thus allowing the corticosteroid to reach the peripheral airways. This also was demonstrated in other studies.[26-28]

Currie et al. assessed 20 adult asthmatic patients in a randomized double-blind study and observed that fluticasone-HFA and its combination with salmeterol were efficient in reducing PD20 (dose that caused a 20% decrease in FEV_1), but only fluticasone-salmeterol improved the FEV_1, FEF_{25-75} and the morning peak flow, and so, the conclusion was that this combination allows the improvement in bronchial hyperresponsiveness and in airway caliber, whereas the isolated use of the corticosteroid acts only upon the former parameter. The fluticasone-salmeterol combination may result in larger peripheral deposition of the corticosteroid in the lung, which improves its anti-inflammatory action on small airways.[29]

Another alternative is non-extrafine HFA, a registered trademark of Modulite®. Modulite® also uses HFA 134a as a propellant, but in this case, a nonvolatile solvent, glycerol, is added, which produces larger particles whose size resembles that of CFC particles. Moreover, the jet orifice diameter was increased, making the spray plume similar to that of CFC.[30,31] Nowadays, BDP-Modulite® and budesonide-Modulite® are available in the international market The advantage of Modulite® technology is that it bears a striking resemblance to the pMDI that use CFC propellant. This allows the CFC/HFA transition to be more easily planned, since it is not necessary to change the doses used, as pulmonary deposition and absorption are similar to those of CFC-containing pMDI because the particle size is similar.[32]

CFC- and HFA-containing pMDI: pharmacokinetic differences

Gross et al.[33] show that adult patients with moderate asthma who remained symptomatic while receiving low doses of CFC-BDP (800 µg/day) could be managed with a smaller dose of HFA-BDP (400 µg/day). This dose of HFA also revealed significant advantages over the placebo ($p \leq 0.003$). The authors mention some advantages of HFA-BDP over CFC-BDP, such as: a possible reduction in treatment costs, as half the recommended dose of CFC-BDP is used; fewer local side effects (dysphonia, candidiasis) due to a lower effective dose and to the reduction in the deposition of the drug in the oropharynx; fewer systemic side effects (hypothalamic-pituitary-adrenal axis suppression, purpura, osteopenia); and larger deposition in the peripheral airways.[33]

Furthermore, Magnussen et al. assessed bronchial hyperresponsiveness to histamine as an additional parameter for the monitoring of inhaled corticosteroid therapy in asthmatic patients. A multicenter, randomized, double-blind study analyzed 164 adult patients who used 1,000 µg of CFC-BDP in the four-week run-in period. Of the 150 patients admitted to the second phase, 72 continued to receive the same treatment and the remaining 78 began to receive 400 µg of HFA-BDP. No statistically significant differences were noted between the two groups in relation to the symptoms, pulmonary function, airway hyperresponsiveness and serum markers of inflammation at the end of the run-in period and at the end of the second phase.[34]

Recent studies have demonstrated that the inflammatory process in asthma occurs both in large and small airways, in addition to the remodeling that occurs in the latter.[9,35] This remodeling may be accountable for the enhanced resistance of small airways, even in asymptomatic patients. The clinical meaning of small airway involvement in asthma, contribution to a fatal outcome or to a rapid decrease in pulmonary function is still uncertain, but, if confirmed, it would be one more advantage of HFA-BDP, since this preparation reaches the peripheral airways more easily.[9,35]

Efficacy, safety and tolerance of drugs combined with HFA

The physical characteristics of the HFA-BDP extrafine aerosol spray allow the medication to evenly reach the large, intermediate and small airways. This distribution of medication allows reducing the nominal dose comparatively to CFC-BDP via a pressurized inhaler, maintaining an efficiency that is comparable to that of fluticasone-CFC. This extrafine spray plume has another advantage: it does not produce serum or tissue accumulation when given at 12-hour intervals between doses. On top of that, even when the maximum daily dose (800 µg) is exceeded, it does not seem to cause relevant systemic side effects.[36]

A recent review on small airway inflammation in asthmatics, published by Cruz & Ponte, points out that the inflammation may result in significant clinical consequences,

such as airway remodeling and irreversible obstruction, and that, therefore, it may be necessary to find alternatives to treat inflammation in this region of the lung. The use of inhaled corticosteroids using an HFA-containing pMDI is an alternative in this case.[37]

Table 1 summarizes the major studies about the efficacy of pMDI containing HFA as a propellant, and presents relevant information such as author and country, year of publication, type of drug, study design, sample size and age group.

The studies listed in the table provide information about the efficacy of the drugs combined with HFA. Note that most studies on HFA use BDP. Some studies have assessed salbutamol, fluticasone, flunisolide and the combination of fluticasone and salmeterol. Only two studies have exclusively evaluated pediatric patients.

Extensive tests have been performed in order to evaluate the safety and tolerance of HFA-BDP. No significant adverse effects were expected as BDP has been used for more than 30 years. However, some differences were noted due to the lower deposition in the oropharynx and larger deposition in the lungs obtained with HFA.[39]

It is common knowledge that inhaled corticosteroids, especially in high doses, may cause hypothalamic-pituitary-adrenal axis suppression. The average percentage of changes in the 24-hour urinary cortisol excretion of 43 adult asthmatic patients shows that the maximum recommended dose of HFA-BDP 640 µg/day produced the same adrenal suppression as the dose of 672 µg/day of CFC-BDP, which is considered to be intermediate.[40]

The meta-analysis conducted by Lipworth involving four studies that compared HFA-BDP with CFC-BDP indicates that there is no clinically significant adrenal suppression when HFA-BDP is used in lower doses than the minimum recommended daily dose (640 µg/day).[36]

The same result was obtained by Pedersen et al., in whose study 300 children aged between 6 and 11 years used HFA-BDP and CFC-BDP for12 months, but no significant differences were observed regarding growth rate ($p = 0.796$), frequency of asthma attacks ($p = 0.517$), upper respiratory infections ($p = 0.335$) or worsening of asthma symptoms ($p = 0.759$).[38]

Table 1 - Major studies about the efficacy of pMDI containing HFA

Author/ Country	Drug	Design	Asthma severity	Sample size	Age group	Conclusion
Gross et al., USA[33]	Beclomethasone dipropionate	Controlled clinical trial	Mild and moderate	347	18-65	Efficacy of HFA-DPB similar to CFC-DPB using half dose
Farmer et al., UK, South Africa, Servia[35]	Beclomethasone dipropionate	Controlled clinical trial	Mild and moderate	229	7-12	Efficacy of HFA-DPB similar to CFC-DBP using half dose
Leach et al., USA[12]	Beclomethasone dipropionate	Controlled clinical trial	Mild	9	18-55	Better pulmonary deposition of HFA-DPB comparing to FP-CFC and CFC-DPB
Fowler et al., UK[24]	Fluticasone propionate	Controlled clinical trial	Mild and moderate	18	16-70	Efficacy of FP-HFA similar to FP in powder inhalers
Langley et al., UK[25]	Fluticasone propionate	Controlled clinical trial	Mild and moderate	59	21-41	Efficacy of FP-HFA similar to FP in powder inhalers
Bousquet & Cantini, France[32]	Dipropionato de beclometasona	Controlled clinical trial	Mild and moderate	1,158	15-44	Equivalent doses of HFA-DPB and CFC-DPB make the transition easier
Pedersen et al., Denmark[38]	Beclomethasone dipropionate	Controlled clinical trial	Mild	300	5-11	Efficacy of HFA-DPB similar to CFC-DPB using half dose
Hauber et al., Canada[26]	Flunisolide	Controlled clinical trial	Mild and moderate	12	18-50	Suppression of eosinophil inflammation of peripheral and entral airways with improvement in pulmonary function
Currie et al., UK[29]	Fluticasone-salmeterol	Controlled clinical trial	Mild	14	32-40	Similar efficacy between HFA-DPB and fluticasone-HFA with the same dose

HFA costs

A multicenter randomized trial including groups of patients from the USA, the UK, Netherlands and Belgium showed, after one year, that the cost of the maintenance of inhalation therapy per patient with chronic asthma is not reliant upon the type of propellant used (CFC or HFA), with an estimated annual cost of US$ 225.62 for the HFA-BDP group, which was slightly lower than that for the CFC-BDP group (US$ 321.07). HFA-BDP showed a larger percentage (42.4%) of asymptomatic days compared with the CFC-BDP group (20%), with a statistically significant p value ($p = 0.006$). When assessing the average cost of each asymptomatic day, HFA propellant proved more economical, with a cost of US$ 1.36 compared to US$ 1.81 for the CFC-BDP group. Therefore, the authors concluded that the management of chronic asthma with HFA would have a lower cost.[41]

A group led by Gross conducted a multicenter, randomized, blind study with 347 adult asthmatics and found out that those being treated with HFA-BDP, at a dose of 400 µg, were managed in the same fashion as those who used CFC-BDP at 800 µg, and their conclusion was that there is some cost reduction.[33]

It should be underscored that there is a paucity of studies on the cost effectiveness of asthma treatment and that the methodologies used vary. Therefore, new studies should be carried out, especially in Brazil.

CFC/HFA transition period and publicizing of information

An interesting fact about the necessity to replace CFC with HFA was pointed out by Donohoe et al. in the United Kingdom: lack of information about this replacement among patients who use pMDI and among health professionals. The study revealed that 60% of the interviewed patients were not aware of the change, which shows that it is necessary to publicize it and clarify it on a large scale, since British authorities believe that the replacement of propellants in pMDI will be the most important change in the composition of a medication ever in the United Kingdom and may bring instability in the management of asthma, thus demanding special attention from health professionals.[42]

Hartung et al. report the results of a study in which 100 patients were interviewed about the replacement of CFC-containing pMDI with HFA-containing pMDI or with powder inhalers. They found that 96 patients did not have any problems with accepting the change, but they observed that some of them (four patients) preferred powder inhalers, despite the fact that this type of inhaler costs three times more. Finally, the authors suggest that physicians should use the CFC/HFA transition period to reassess the treatment and inhalation technique of their patients.[43]

Final remarks

New treatment options that have arisen in the last few years have revolutionized the treatment of asthma in all age groups. What these new options share in common is that they are administered by inhalation, which allows optimizing the efficacy/tolerance ratio in the treatment of asthma. The most widely used alternatives for the inhalation of asthma medications are powder inhalers and pMDI.

CFC phaseout encouraged the search for new asthma treatments. CFC-BPD-containing pMDI result in deposition of the drug mainly in the oropharynx, causing undesirable oral absorption, and not properly reaching the inflammation of the distal airways. HFA-BPD provides larger lung deposition, although inhalation is not the ideal technique, allowing the use of a lower daily dose of corticosteroid. HFA-BPD is efficient, well tolerated and does not cause clinically significant hypothalamic-pituitary-adrenal axis suppression when given in the recommended doses.

The CFC/HFA transition period should be regarded as an opportunity to reassess patients, taking into account not only the asthma management, but also the patient's quality of life and the proper inhalation technique, for optimal medication use.

Most studies on HFA use BPD and are carried out with adults. Some studies also assess salbutamol, fluticasone, flunisolide and the combination of fluticasone and salmeterol. Further studies are necessary to assess the efficacy and tolerance of HFA-containing pMDI in all age groups, including other drugs that had been used in combination with CFC, such as budesonide, formoterol, ipratropium bromide and fenoterol. The studies on HFA-BPD may be considered to be sufficient to assess the tolerance of HFA as a propellant, but the results obtained in these studies regarding the observed pharmacokinetic advantages cannot be safely extrapolated, as these advantages are specifically related to the physical characteristics of the HFA-BPD particles. In Brazil, fluticasone-HFA and fluticasone-salmeterol-HFA formulations are already commercially available. However, due to the paucity of studies about the use of HFA in pediatric patients, further controlled research should be conducted with children and adolescents.

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Corresponding author:
Paulo Augusto Moreira Camargos
Departamento de Pediatria, Faculdade de Medicina, UFMG
Av. Professor Alfredo Balena, 190/4061
CEP 30130-100 – Belo Horizonte, MG
Brazil
Phone: +55 (31) 3248.9772
Fax: +55 (31) 3248.9664
E-mail: pcamargs@medicina.ufmg.br