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The oropharyngeal and lung deposition patterns of a fusafungine MDI spray delivered by HFA 134a propellant or by CFC 12 propellant

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Abstract

We report for the first time the deposition pattern in the respiratory tract of a metered dose inhaler formulated with hydrofluoroalkane (HFA) 134a, in comparison with an inhaler containing chlorofluorocarbon (CFC) 12. The inhalers delivered 125 μg fusafungine per metered dose, and deposition was assessed using the non-invasive technique of gamma scintigraphy. Preliminary in vitro validation studies showed that the ^{99m}Tc tracer acted as a good marker for the distribution of fusafungine. The in vivo study was carried out in 10 healthy volunteers who each inhaled a single dose of radiolabelled fusafungine on two occasions. The majority of the dose from the HFA 134a and CFC 12 fusafungine formulations was deposited in the oropharynx (mean 65.7 and 64.3%, respectively), with an average of only 2.4 and 3.2% deposited in the lungs. It was concluded that the deposition pattern for the new fusafungine formulation with HFA 134a propellant is similar to that of the existing formulation containing CFC 12.

Keywords: Chlorofluorocarbon; Hydrofluoroalkane; Metered dose inhaler; Gamma scintigraphy; Lung deposition; Oropharyngeal deposition

The pressurised metered dose inhaler (MDI) using chlorofluorocarbon (CFC) propellants is a convenient and well proven method of producing aerosols for delivery of inhaled drugs to the respiratory tract. However, CFCs are known to contribute to ozone layer depletion (Molina and Rowlands, 1974), and there is a prohibition on their production, which has led to the reformulation of MDIs with hydrofluoroalkanes (HFAs). This reformulation may change the deposition pattern in the respiratory tract. In this study we report for the first time the deposition pattern of an HFA-based pressurised aerosol, compared to that of the CFC-based aerosol which it is replacing.

The present gamma scintigraphic study was designed to compare the oropharyngeal and lung deposition patterns of a throat spray containing

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fusafungine (125 μg per 50 μl dose, Locabiotal, Servier) delivered from MDIs containing either HFA 134a or CFC 12 propellant. Fusafungine is an antibiotic with anti-inflammatory properties produced from *Fusarium lateritium* (German-Fattal, 1989; German-Fattal and German, 1990), which is used for the topical treatment of nasal, mouth and throat infections. Both formulations contained alcohol, isopropyl myristate and saccharin, and were radiolabelled with ^{99m}Tc (10 MBq per dose) using a previously established technique (Newman et al., 1989,1991; Summers et al., 1990).

Prior to commencement of the in vivo study, the radiolabelling technique was validated for both MDI formulations. A multistage liquid impinger comprising a 'throat', four impaction stages and a final filter was used to demonstrate that the particle size distribution within the aerosol cloud was unaffected by the radiolabelling process, and that the distribution of ^{99m}Tc tracer within the impinger apparatus mirrored that of the fusafungine for both the HFA 134a and CFC 12 formulations (Table 1). The mean percentage distribution of drug from the non-radiolabelled and radiolabelled MDIs (designated 'unlabelled' and 'labelled' drug, respectively), and the distribution of radiolabel on the various stages of the impinger were similar for both the HFA 134a and CFC 12 fusafungine formulations (Table 1). As expected with formulations intended primarily for oropharyngeal deposition, the percentage of drug contained in fine particles smaller than 5 μm diameter was < 10% of the dose for both formulations.

10 healthy volunteers (six male, four female; age range 21–58 years) with lung function values ≥ 80% of the predicted value for their age, sex and height completed the study. The nature of the study was explained both in writing and verbally to each volunteer, and written consent was obtained. A list of detailed inclusion and exclusion criteria were agreed prior to volunteer recruitment, and each subject underwent a medical examination prior to entering and after completing the study. The study was approved by an Ethics Committee. Each subject inhaled a single dose of 125 μg fusafungine on two separate occasions. In vivo deposition patterns were assessed from scans of the lungs and oropharynx (General Electric Maxi gamma camera coupled to a Bartec Micas V data processing system). Retention on the actuator and on an exhaled air filter was also assessed.

The deposition pattern (Table 2) was similar for both formulations, and was in keeping with that of formulations specifically designed for treatment of throat infections, where oropharyngeal deposition rather than lung penetration is of primary importance. The major part of the metered dose from both the HFA 134a and the CFC 12 fusafungine formulations was deposited in the oropharynx, with the remaining dose divided between the actuator, lungs (2.4 and 3.2%, respec-

Table 1
Mean (SD) percentage distribution of drug from unlabelled and radiolabelled MDI canisters, and distribution of radiolabel ($n = 4$)

Site	Fusafungine CFC 12 formulation			Fusafungine HFA 134a formulation		
	Unlabelled [a] drug	Radiolabelled [b] drug	Radiolabel	Unlabelled [a] drug	Radiolabelled [b] drug	Radiolabel
Actuator	14.7 (2.1)	11.1 (2.5)	11.0 (2.8)	15.9 (2.3)	17.0 (2.0)	17.3 (3.1)
Throat	71.7 (1.3)	78.1 (2.5)	79.9 (2.8)	70.3 (6.0)	70.0 (4.6)	71.2 (4.7)
Stage 1	2.3 (1.8)	1.6 (0.2)	1.9 (0.4)	2.1 (1.0)	3.0 (1.9)	3.9 (3.1)
Stage 2	2.0 (0.3)	1.7 (0.1)	1.3 (0.3)	1.9 (0.7)	1.8 (0.4)	1.5 (0.5)
Stage 3	2.7 (0.2)	2.2 (0.2)	1.6 (0.2)	2.6 (0.7)	2.3 (0.5)	1.9 (0.3)
Stage 4	6.1 (0.4)	4.8 (0.2)	4.2 (0.6)	6.5 (1.5)	5.2 (0.8)	4.3 (0.5)
Final filter	0.6 (0.1)	0.6 (0.0)	0.1 (0.1)	0.7 (0.1)	0.9 (0.2)	0.0
RF	9.4	7.6	5.9	9.8	8.4	6.2

RF, mean respirable fraction (sum of stages 3, 4 and the final filter).
[a] Drug fired from unlabelled MDI canisters.
[b] Drug fired from radiolabelled MDI canisters.

Table 2
Summary of the mean (SD) deposition data for fusafungine MDI formulations containing HFA 134a and CFC 12 propellants ($n = 10$)

Formulation	Percentage of metered dose			
	Oropharynx	Lung	Actuator	Exhalation filter
HFA 134a	65.7 (7.1)	2.4 (1.0)	31.3 (7.6)	0.6 (0.6)
CFC 12	64.3 (7.0)	3.2 (1.0)	31.6 (7.3)	0.9 (1.1)

tively), and trapped on the exhalation filter (Table 2). Other MDI formulations using CFC propellants and specifically designed to deliver aerosolised drug into the lower respiratory tract have shown higher values for both in vitro respirable fraction and in vivo lung deposition (Newman et al., 1989, 1991; Biddiscombe et al., 1993).

Subjects were taught to inhale according to the recommended method for optimal use of MDIs (Newman, 1982). An investigator fired the device shortly after the start of the inhalation manoeuvre. The average inhalation flow rate was recorded for each subject during dosing using a Vitalograph MDI Compact Spirometer (mean 25.6 l min^{-1} and 24.3 l min^{-1} for the HFA 134a and CFC 12 formulations respectively). Inhaled volumes and breath-holding pauses were also similar for the two treatment regimens, indicating that the same inhalation technique was used for both formulations.

The similarity in the deposition patterns suggests that both the HFA 134a and the CFC 12 formulations behave in a similar manner in vivo when fired from an MDI, and that HFA 134a propellant provides a viable alternative to CFC 12 for the delivery of fusafungine. This study is the first occasion on which the deposition patterns of HFA-based and CFC-based MDI formulations have been compared directly, and indicates that the technique of gamma camera scintigraphy can be used to demonstrate similar degrees of pulmonary bioavailability for two inhaled products.

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