J. Pharm. Pharmacol. 1995, 47:818–821
Received March 17, 1995
Accepted July 11, 1995

Scintigraphic Assessment of the Oropharyngeal and Nasal Depositions of Fusafungine from a Pressurized Inhaler and from a Novel Pump Spray Device

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Abstract

The distributions of fusafungine (Locabiotal, Servier) radiolabelled with ^{99m}Tc, and delivered either orally or intranasally, have been assessed in healthy volunteers from a pressurized metered-dose aerosol inhaler (125 μg per dose) and from a novel mechanical pump spray device (500 μg per dose).

More than 90% of the dose was initially deposited in the oropharynx for oral dosing (n = 8), and more than 90% in the nose for nasal dosing (n = 9), with no significant penetration of aerosol into the lungs. Although not statistically significant, the mean area of deposition, measured in terms of gamma camera picture elements (pixels), was greater with the pump spray for both oral and nasal dosing. The area of deposition with the nasal pump spray extended into the turbinates in six of nine subjects, compared with only three of nine subjects for the pressurized aerosol.

The data suggest that the distribution patterns of pump sprays and pressurized aerosols of fusafungine in the oropharynx and in the nasal passages are similar, and that the former can be substituted for the latter with little change in drug delivery.

Fusafungine is an antibiotic with anti-inflammatory properties, of fungal origin produced by *Fusarium lateritium*, and is used as a topical agent for the treatment of infections and inflammatory conditions of the upper respiratory tract (German-Fattal 1989; German-Fattal & German 1990). The formulation approved for use (Locabiotal, Servier) is a pressurized aerosol using chlorofluorocarbon 12 (CFC 12) as the propellant, but CFCs are being phased out during the second half of this decade owing to the environmental problems which they cause (Newman 1990), and alternative delivery systems must be sought. A new formulation of fusafungine has been developed that does not require CFCs, delivered as a spray by a hand-operated mechanical pump. Since fusafungine is a topically acting agent, and is not detectable in the plasma when administered by inhalation to man, a standard bioequivalence study would be an inappropriate means of comparing two formulations of this compound. Thus in order to assess the similarity of the distributions in the upper airways between the pressurized aerosol and the pump spray, the deposition patterns in the oropharynx and nasal passages have been assessed by the technique of gamma scintigraphy.

Materials and Methods

Pressurized aerosols and mechanical pump sprays delivering fusafungine (Locabiotal, Servier) were radiolabelled by the addition of the radionuclide ^{99m}Tc (Newman 1993a). For the pressurized aerosol, the radiolabel was extracted from the aqueous phase in butanone, placed in an empty canister, and evaporated to dryness. The contents of a filled canister containing the drug formulation in CFC 12 were added at −60°C. A metering valve was sealed onto the canister by a crimper. For the pump spray formulation, 10 mL fusafungine solution was added to a vial containing ^{99m}Tc which had been prepared in the same manner as for the pressurized aerosol. A metering valve was added, and the contents were shaken to disperse the radiolabel uniformally. For oral use, each metered dose from pressurized aerosol or pump spray delivered 5 MBq ^{99m}Tc per dose, compared with 1 MBq ^{99m}Tc for nasal use. The pressurized aerosol and pump spray delivered 125 and 500 μg fusafungine per metered dose, respectively. The metered dose volume was 50 μL for both devices, and both formulations contained alcohol, saccharin, isopropyl myristate and flavouring agents.

Eleven healthy volunteers (5 males, 6 females, age range 20–46 years) entered the study (Table 1). All had lung function within the normal range (forced expiratory volume in 1 s, FEV1, $\geqslant$ 80% of the value predicted on the basis of age, sex and height (Quanjer et al 1993)). Volunteers were non-smokers of at least 12 months duration, without any significant history of respiratory, nasal or oral disease. Each subject underwent a medical examination within 21 days of entering and within 14 days of completing the study. Before recruitment, the nature of the study was explained both orally and in writing to each volunteer, and written consent was provided. The study was conducted according to the Declaration of Helsinki. The study protocol was approved by the Quorn Research Review Committee, Leicestershire, UK, and the Department of Health (UK) gave approval for the administration of the radioactive fusafungine sprays.

The study was divided into two separate randomized, single blind, two-way cross-over trials, the first to determine oral deposition of fusafungine, and the second to determine

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Table 1. Subject details, including forced expiratory volume in one second (FEV1) measurements made at the time of the pre-study medical screening. Eight subjects were dosed via the oral route, and nine via the nasal route.

Subject number	Dosing route	Age (years)	Sex	Height (cm)	Weight (kg)	FEV1 (L) (measured)	FEV1 (L) (predicted)	FEV1 (% predicted)
1	Both	22	F	170	60	3·21	3·49	92
2	Both	46	F	168	60	2·96	2·89	102
3	Nasal	22	M	175	67	3·67	4·31	85
4	Both	20	M	178	71	4·50	4·44	101
5	Oral	20	F	161	55	2·97	3·13	95
6	Both	23	M	183	86	4·27	4·65	92
7	Both	46	F	166	67	3·01	2·81	107
8	Nasal	24	F	172	67	3·64	3·57	102
9	Both	38	M	172	72	3·64	4·11	89
10	Oral	31	M	178	86	4·43	4·27	104
11	Nasal	31	F	164	73	2·98	3·10	96

nasal deposition. Eight of the subjects (4 males, 4 females, age range 20–46 years, FEV1 range 89–107% predicted) received both the pressurized and pump sprays by the oral route, while nine of the subjects (4 males, 5 females, age range 20–46 years, FEV1 range 85–107% predicted) received both sprays via the nose. A minimum of 48 h elapsed between any two dosings with fusafungine. A single dose of either 125 μg fusafungine by pressurized aerosol, or 500 μg by pump spray was administered on each study day. The devices used for oral and nasal deliveries were identical, but were fitted with a mouthpiece or a nasal adaptor as appropriate. Before administration of the radiolabelled aerosol in the oral delivery study, subjects practised the inhalation manoeuvre to be used with the aid of a placebo device. Subjects were taught to make a normal inhalation co-ordinated with the firing of the device, and then to exhale through the nose, so that any exhaled radioactivity could be trapped on a cotton wool nose-plug taped across the nostrils. In the nasal delivery study, the aerosol was delivered into the right nostril, whilst the subject held the left nostril closed with a finger. Nasal delivery was practised without the administration of placebo, to avoid any local irritation before administration. Once the subject could reproducibly perform the correct inhalation manoeuvre, the appropriate radioactive formulation was administered, with the inhaler actuated by an investigator approximately 1 s after the subject started inhaling. To minimize possible effects of the nasal cycle (Hasegawa & Kern 1977) on drug delivery, successive nasal dosings for each subject were carried out at approximately the same time of day. Before use, the mechanical pump actuators were primed five times.

Immediately following administration of the radiolabelled aerosol, scintigraphic images of 100-s duration were recorded using a General Electric Maxicamera, coupled to a Bartec data processing system, of the right lateral view of the head, the anterior view of the chest, the posterior view of the chest, and images of the actuator, mouthpiece and nose-plugs (where appropriate). The chest views were taken to quantify any radioactivity which had been swallowed and to look for the presence of radioactivity in the lungs. Counts were corrected for background radiation, radioactive decay and for attenuation of gamma rays by tissue. In regions where both anterior and posterior views were recorded, the geometric mean of counts in both images was calculated. In the oral study, the emitted dose was fractionated into amounts in the mouth and pharynx, retained on the actuator mouthpiece, and recovered from the nose-plugs. In the nasal study, the emitted dose was fractionated between the nasal passages and the nasal adaptor. Swallowed activity in the oesophagus or stomach was assumed to have been deposited in the mouth or the nose. The number of gamma camera picture elements (pixels) within a contour marking 5% of peak activity was determined on the oropharyngeal and nasal images, to ascertain the area of initial deposition.

In both the oral study and the nasal study, the Wilcoxon matched-pairs signed-ranks test was used to compare the distributions of the dose and the number of pixels for the pressurized aerosol compared with the pump sprays (Siegel & Castellan 1988). A P value of 0·05 was taken to indicate statistical significance.

Results

Oral study

The fractionation of the dose in the oral study (Table 2) was similar for pressurized aerosol and for pump spray. A mean value of 93·8% (range 88·3–99·6%) of the emitted dose from the pressurized aerosol was deposited in the oropharynx, with a mean ± s.d. value of 39·9 ± 15·1% of the dose being recorded over oesophagus and stomach. For the pump spray, a mean 91·9% (87·8–98·5%) of the emitted dose was deposited in the oropharynx, with a mean value of 47·0 ± 11·0% of the dose recorded over oesophagus and stomach. The remainder of the dose not deposited in the

Table 2. Fractionation of the emitted dose in the oral study, and number of pixels covered by the initial deposition site. Data are mean ± s.d., n = 8.

	Pressurized aerosol	Pump spray
Oropharynx[a]	93·8 ± 3·7	91·9 ± 3·9
Mouthpiece	6·0 ± 3·7	8·1 ± 3·9
Nose-plugs	0·3 ± 0·2	0·0 ± 0·0*
Number of pixels	350 ± 141	404 ± 139

[a] Including swallowed activity in oesophagus and stomach.
*P = 0·05 compared with pressurized aerosol.

Table 3. Fractionation of the emitted dose in the nasal study, and number of pixels covered by the initial deposition site. Data are mean ± s.d., n = 9.

	Pressurized aerosol	Pump spray
Nose[a]	97·7 ± 1·7	97·0 ± 2·1
Nasal adaptor	2·3 ± 1·8	3·0 ± 2·1
Number of pixels	129 ± 41	168 ± 54

[a]Including swallowed activity in oesophagus and stomach.

mouth was either retained on the mouthpiece, or recovered from the nose-plugs, but the latter was less than 0·5% of the dose. With the exception of the nose-plugs, the differences between the devices were not statistically significant. No significant counts above background were detected from the lungs. The deposition area covered by the fusafungine did not differ significantly between the two devices. For the pressurized aerosol, a mean 350 pixels (range 266–620 pixels) was covered by the initial deposit, which was located in the mouth in five subjects, the mouth and pharynx in two subjects and in the pharynx in one subject. For the pump spray, a mean 404 pixels (range 213–570) was covered initially, and the deposition area was located in the mouth in three subjects and in the mouth and pharynx in the remaining five subjects.

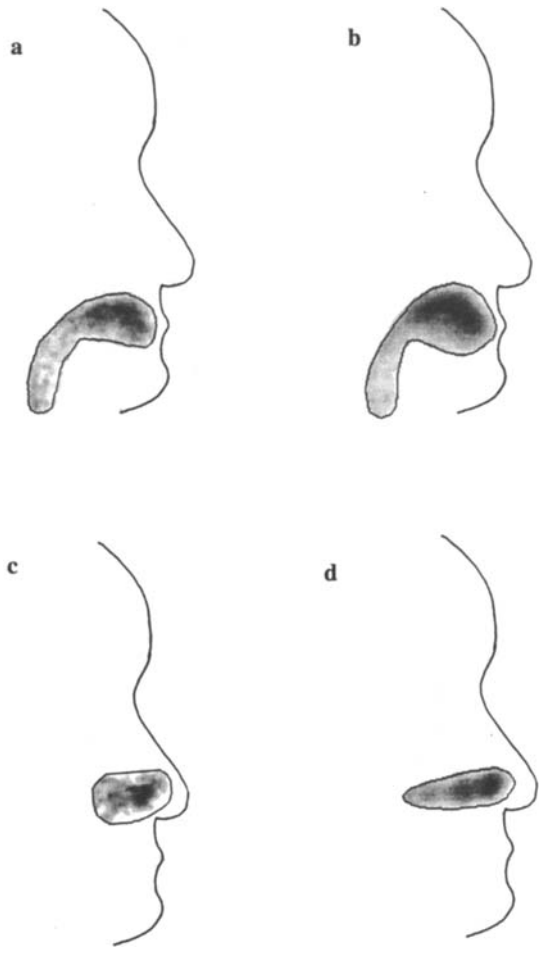

FIG. 1. Initial distribution patterns of radiolabelled fusafungine aerosol in one subject. a. Pressurized aerosol, oral; b. pump spray, oral; c. pressurized aerosol, nasal; d. pump spray, nasal. The contour marking 5% of peak activity is shown on the scans.

Table 4. Mean ± s.d. values of forced expiratory volume in one second (FEV1, L) immediately pre-dosing, and 30 min post-dosing.

Device	Route	n	Pre-dose	Post-dose
Pressurized aerosol	Oral	8	3·64 ± 0·67	3·66 ± 0·68
Pump spray	Oral	8	3·66 ± 0·73	3·67 ± 0·75
Pressurized aerosol	Nasal	9	3·55 ± 0·57	3·57 ± 0·61
Pump spray	Nasal	9	3·60 ± 0·62	3·55 ± 0·63

Nasal study

The fractionation of the dose in the nasal study (Table 3) was also similar for the two formulations. A mean 97·7% (range 95·0–99·9%) of the emitted dose from the pressurized aerosol was deposited in the nose, with a mean value of 1·1 ± 1·3% of the dose being recorded over oesophagus and stomach. For the pump spray, a mean 97·0% (range 93·3–99·5%) of the emitted dose was deposited in the nose, with a mean value of 2·4 ± 4·2% of the dose recorded over oesophagus and stomach. As in the oral study, counts from the lungs did not exceed background levels. Analysis of the deposition within the nose showed a trend towards a larger deposition area for the pump spray, but this was not statistically significant. For the pressurized aerosol, a mean 129 pixels (range 76–185) was covered by the initial deposit, compared with a mean 168 pixels (range 91–268) for the pump spray. However, it was noticeable that with the pump spray formulation, the site of impaction extended from the nasal valve into the turbinates in six of the nine subjects, reaching the nasopharynx in one subject, whereas with the pressurized aerosol, the major site was at the nasal valve (in six of nine subjects), with an extension into the turbinates being observed only in three subjects. Times of days of successive dosings for the nine subjects differed by the following amounts: 2, 2, 3, 5, 6, 10, 19, 31 and 72 min.

Typical scans for showing distributions of the dose after oral and nasal dosings are shown in Fig. 1. Comparison of spirometric data before dosing and at 30 min after delivery of fusafungine showed no clinically significant effect on lung function either for oral or nasal dosing (Table 4).

Discussion

Although the deposition in the oropharynx and in the lungs of pressurized aerosols used for asthma therapy have been studied extensively (Newman 1993a, b), there are few data available on the deposition of sprays intended for upper airway therapy alone. When fusafungine was given orally, the majority of the dose was deposited in the oropharynx by inertial impaction, although approximately half of this was rapidly swallowed and was located in the oesophagus and stomach. The distribution of the dose in the oropharynx, assessed in terms of the number of gamma camera pixels covered by the deposit, suggested a slightly larger deposition area for the pump spray, but the difference with the pressurized aerosol was not significant. Examination of the scans

showed that the area of deposition was confined to the mouth for some of the volunteers, but penetrated into the pharynx for other subjects.

When fusafungine was given intranasally, more than 90% of the emitted dose was deposited in the nasal cavity, and virtually none of this was detected over oesophagus and stomach. Analysis of the deposition patterns showed that the maximum deposition for both formulations occurred in the area of the nasal valve, which has the narrowest cross-section of any part of the respiratory tract (Proctor 1982, 1985). Drug penetrating distally into the nose may be cleared by the mucociliary mechanism, while retention of drug deposited more proximally is prolonged (Bond et al 1984; Hardy et al 1985). Although the area covered by the two sprays expressed in terms of gamma camera pixels did not differ significantly between the two formulations, there was a trend towards coverage of a larger area with the pump spray, and the area of maximum deposition extended into the turbinates in six subjects with pump spray, compared with only three subjects for the pressurized aerosol. Previous studies (Newman et al 1987a, b) have suggested that sprays from pump devices may be deposited over a greater area of the nasal mucosa than pressurized aerosols, probably because the more slowly moving droplets from the pump spray are better able to penetrate beyond the nasal valve. Further studies have shown that the deposition in the nasal passages from a multidose powder inhaler (Turbuhaler) resembled those from a pressurized aerosol (Thorsson et al 1993), while the distribution of an aqueous spray containing insulin was dependent upon the size of the metered dose, but did not vary according to whether a slow or rapid inhalation was taken (Newman et al 1994).

No radiolabel was detected in the lungs in any study. For nasal delivery, this is not surprising, since the nose is a very efficient filter of aerosol particles and droplets (Heyder & Rudolf 1975). Further, the aqueous sprays generated by mechanical pump action usually contain virtually none of the dose in particles smaller than 10 μm diameter (Petri et al 1985). Particles or droplets smaller than 5 μm are generally considered to comprise the respirable range (Heyder & Rudolf 1975). Some penetration of the pressurized aerosol into the lungs when given orally might have been expected, but the respirable fraction of this formulation (the percentage of the drug mass contained in particles smaller than about 5 μm, and which could thus on theoretical grounds be inhaled) is only about 5% (unpublished observations). Further, the sprays were inhaled during a normal breath, and not by an optimal technique of deep breathing and breath holding (Newman et al 1982). Even with an optimal inhalation technique, no more than 15% of the dose from a pressurized aerosol typically reaches the lungs, and this figure is reduced further when inhalation is suboptimal or when the spray contains few small droplets suitable for inhalation.

In conclusion, these studies have shown that similar distributions of a fusafungine formulation are obtained in either the mouth or in the nose from a novel pump spray and from a pressurized aerosol, suggesting that the former can be used to replace the latter with little change in drug delivery.

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