Systemic availability of budesonide after nasal administration of three different formulations: pressurized aerosol, aqueous pump spray, and powder

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Aims The present study was undertaken to determine the absolute systemic availability of budesonide from three different devices for nasal administration: pressurized aerosol, aqueous pump spray, and powder.

Methods Sixteen healthy, non-smoking, volunteers participated in this open, randomized, and crossover study. All subjects received budesonide as an intravenous dose of 400 µg, and as three, single-dose, intranasal administrations: pressurized aerosol 800 µg, aqueous pump spray 400 µg, and powder 800 µg. Blood was sampled for 10 h after each administration and budesonide was assayed in plasma by liquid chromatography plus mass spectrometry.

Results The mean [95% CI] systemic availability of budesonide with reference to the metered dose was: 13 [10; 15]%, 29 [23; 37]%, and 20 [16; 23]%, and the maximum plasma concentration ($C_{\max}$) was attained at ($t_{\max}$) 2.0, 0.7, and 0.4 h after administration for the pressurized aerosol, aqueous pump spray, and powder, respectively.

Conclusions The uptake of budesonide was more rapid and more complete, and the systemic availability of the drug was significantly higher from the aqueous pump spray and powder than from the pressurized aerosol.

Keywords: budesonide, nasal, systemic availability, pharmacokinetics

Introduction

Rhinitis is effectively treated by nasal administration of glucocorticosteroids (GCSs). The clinical effect of a nasal GCS is elicited by a local action, which has been shown with budesonide [1]. Nasal deposition, primarily caused by impaction of drug particles or droplets on the nasal mucosa, is thus a prerequisite. The site and extent of impaction are affected by the size and the speed of the particles/droplets and may therefore differ between formulations and devices. The aerosol generated from a pressurized metered dose inhaler (pMDI) has a high velocity and is highly directional, resulting in a narrow, proximal deposition in the nasal cavity [2]. The aerosol from the aqueous pump spray is characterized by a large droplet size, and gives a more widespread deposition [3]. The deposition pattern of budesonide powder via Turbuhaler is between that of the other two devices [4].

The systemic availability of budesonide after nasal instillation of an experimental solution, containing pH

regulating additives (pH=5), preservatives and 10% (w/w) Tween 20, was found to be 100%. The complete systemic uptake indicates that no local metabolism of the drug occurred in the nose [5]. With the first budesonide nasal formulation to reach the market, the pMDI, the drug had a systemic availability of 21% with reference to the delivered dose [6]. In clinical studies, budesonide in the aqueous pump spray formulation [7, 8], and in the Turbuhaler® formulation [9], has been shown to have similar anti-rhinitis efficacy to that of the pMDI formulation.

The aim of the present study was to determine the absolute systemic availability of budesonide from three different marketed devices for nasal administration (Rhinocort®); the pMDI, the aqueous pump spray, and Turbuhaler®.

Methods

Subjects

Seventeen healthy volunteers (10 women) were recruited for the study. One subject was excluded after being randomized when it was discovered that she was a

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smoker, as smoking was an exclusion criterion. The mean age was 31 years (range 20–44 years), mean height 172 cm (161–200 cm) and mean weight 67 kg (53–94 kg) for the 16 subjects completing the study. All subjects were healthy as judged from a physical examination and clinical laboratory tests. They were fully informed about the purpose of the study and gave their written informed consent before inclusion. The study was approved by the ethics committee of Lund University and by the Swedish Medical Products Agency.

Protocol

The study was open, randomized and with a crossover design. The subjects were given three nasal and one intravenous formulation of budesonide as single doses with a washout period of at least 6 weeks between the administrations. The subjects were asked to adhere to their normal prandial and everyday habits, but were not allowed to drink alcohol 24 h preceding and during an experimental day. Concurrent therapy with prescribed or nonprescribed medication was normally not allowed, but could be used if necessary and judged by the investigator not to affect the outcome of the study.

The intravenous administration was given as a manual injection of 400 µg budesonide over 8 min. The dose was determined by weighing the syringe before and after the injection. An extra 5 ml saline was given to wash the needle after the injection.

The three nasal administrations were given as single doses of budesonide in alternating nostrils with the opposite nostril held closed. Inhalations via the pMDI (50 µg/actuation) and Turbuhaler® (100 µg/dose) were made at 20 s intervals, to give a total nominal dose of 800 µg. The aqueous pump spray (50 µg/actuation) was administered with an interval of 40 s to give a total nominal dose of 400 µg. The lower dose from the pump spray was chosen for two reasons: 1) it was known from *in vitro* data that the amount of drug retained in the device differed between the three different formulations, indicating a higher dose delivered from the aqueous pump spray than from the other two formulations; 2) the volume of drug suspension from the aqueous pump spray was not to be too large in order to avoid having the dose run out of the nose.

Dose definitions

The *nominal dose* refers to the dose labelled on the formulation. The *metered dose* is defined as the dose leaving the metering unit of the device, as determined for each batch. The *delivered dose* is the metered dose minus the amount of drug retained in the device, e.g. in the pMDI adaptor, the applicator of the pump spray, or

the Turbuhaler® nose-piece. Finally, the *dose-to-subject* is the delivered dose minus any amount of drug recovered on its way from the device to the target organ or exhaled after administration.

Drug losses

The dose-to-subject was estimated for Turbuhaler® and for the aqueous pump spray by subtracting from the delivered dose, the amount of budesonide recovered from a moistened tissue after wiping the outside of the nosepiece, the nose, the face around the nose and the gloves, and from a filter used to collect any amount of budesonide being exhaled. The dose-to-subject was not estimated for the pMDI, as it has previously been shown that losses by exhalation after the pMDI are negligible [2]. Likewise, the fraction escaping the nose by backfiring through the pMDI canister due to increased pressure in the nasal cavity when the propellant gas expands should be small. The delivered dose was therefore used instead of the dose-to-subject for the pMDI formulation.

Assays

Liquid chromatography was used to determine the metered dose from the devices and the amounts of budesonide retained in the devices and recovered from the outer parts of the nose and the surrounding skin, the gloves, and exhalation filters.

Plasma samples, for subsequent determination of the budesonide concentration, were obtained after infusion from a venous catheter in the arm not used for the injection immediately before the administration and at 8 (end of the injection), 15, 30, 45, 60 min and 2, 4, 6, 8 and 10 h after the start of injection. For the nasal administrations, plasma samples were obtained immediately before, and at 10, 20, 30, 45, 60 min and 2, 4, 6, 8, and 10 h after start of administration. The samples were stored frozen at -20°C until analysed using a method of combined liquid chromatography and mass spectrometry [10]. The lower limit of quantification (LOQ) was 0.1 nmol l^{-1} , and the coefficient of variation (CV) was 10–18% within-day, and 7% during the analytical period.

Pharmacokinetic parameters were calculated according to standard, non-compartmental methods. The AUC of plasma concentration *vs* time was calculated by the trapezoidal method up to the last plasma concentration (C_p) which was above or equal to the lower LOQ and then the area under a monoexponential function was defined by linear regression of the terminal plasma concentrations. The terminal elimination rate constant λ_z was calculated for each individual from the intravenous data by linear regression of a subjective selection of data

points on which the log plasma *vs* time curve was approximately linear. $C_{\max}$ denotes the maximum plasma concentration and $t_{\max}$ the corresponding time point. The mean residence time (MRT) was obtained by calculation of the area under the first moment curve (AUMC) by integration of the function $t \cdot C_p$. The MRT was then calculated as $\text{AUMC}/\text{AUC} \cdot \text{infusion time}/2$, and the mean absorption time (MAT) was calculated as $\text{MRT}_{\text{niv}} - \text{MRT}_{\text{iv}}$. The systemic availability (F) was calculated as $\text{AUC}_{\text{niv}} \cdot \text{Dose}_{\text{iv}} / \text{AUC}_{\text{iv}} \cdot \text{Dose}_{\text{niv}}$.

The systemic availability was compared between the formulations by a multiplicative analysis of variance (ANOVA) model with fixed factors subject, period and formulation. Confidence limits (95%) were constructed for pairwise formulation contrasts, and P values ≤ 0.05 were considered to be statistically significant. The results for the systemic availability are expressed as geometric means. Other results are expressed as arithmetic means and s.d.

Results

Dose determinations

The different dose estimations and the various drug losses, as defined earlier, are shown in Table 1 for the three nasal formulations. The deviations of metered dose from nominal dose were within *in vitro* specification limits. The amount of drug retained in the devices and recovered from the outer parts of the nose, the surrounding skin, and the gloves differed markedly between the three nasal formulations. On average, 4.7% of the metered dose was recovered after administration with the aqueous pump spray. This is likely to be derived from wiping of the outside of the nosepiece. The retention in the Turbuhaler® nose-piece *in vivo* was, on average, 50.5% of the metered dose, whereas only 0.4% was recovered from wiping the outer parts of the nose, the surrounding skin, and the gloves. The amount of budesonide recovered on the exhalation filters after administration from Turbuhaler® or the aqueous pump spray was in the order of 1%, i.e. negligible. The retention in the pMDI adapter was on average 38.2% of the metered dose. Neither

wipings, nor exhalation filters were collected in conjunction with the pMDI administration, for reasons described in the methods section.

Pharmacokinetics

The plasma concentration profile after intravenous dosing is illustrated in Figure 1. The mean (s.d.) elimination half-life of budesonide was 2.65 (0.33) h, and the plasma clearance was 1.26 (0.22) l min⁻¹. The mean residence time of budesonide was 2.80 (0.52) h and the volume of distribution at steady-state was 211 (51) l.

Following nasal administration, the plasma concentration profiles showed an earlier and higher peak with the aqueous pump spray and Turbuhaler® than with the pMDI, as illustrated in Figure 2. The shape of the individual curves showed relatively large interindividual variability (data not shown) with absorption peaks ranging from 10 min up to 4 h after administration. The systemic availability of budesonide, the maximum plasma concentration ($C_{\max}$), the time for maximum plasma concentration ($t_{\max}$) and the mean absorption time (MAT) are presented in Table 2.

The systemic availability of budesonide was significantly lower from the pressurized aerosol than from the other two formulations ($P < 0.001$ *vs* both the aqueous pump spray and Turbuhaler®), either with reference to the metered dose or to the dose-to-subject. In addition, with reference to the metered dose, the systemic availability was significantly higher from the aqueous pump spray than from Turbuhaler® ($P < 0.001$). Even though it was not significantly different compared with the aqueous pump spray ($P = 0.12$), Turbuhaler® gave the highest systemic availability with reference to the dose-to-subject.

Discussion

The systemic availability of the pMDI formulation (21% of the dose-to-subject, Table 2) in the present study was in good agreement with the literature. The other two formulations had not been studied previously. The pharmacokinetic parameters derived from the intravenous

Table 1 Dose estimations and the amounts of budesonide retained in the devices and recovered from the outer parts of the nose and the surrounding skin, the gloves, and exhalation filters for three nasal formulations of budesonide (mean and s.d.).

Formulation	Nominal dose (μg)	Metered dose (μg)	Retained + recovered* + exhaled* amount (μg)	Dose-to-subject (μg)
pMDI	800	715 (38)	271 (74)	444 (96) [#]
Aqueous pump spray	400	409 (26)	23 (18)	386 (28)
Turbuhaler ®	800	726 (128)	375 (111)	351 (18)

*Only for the aqueous pump spray and Turbuhaler®.

[#]The delivered dose was used instead of the dose-to-subject for the pMDI formulation.

Figure 1 Plasma concentration profile of budesonide after intravenous administration of 400 µg over 8 min (mean and s.e.mean).

Figure 2 Plasma concentration profiles of budesonide after single-dose nasal administrations of pressurized aerosol 800 µg (---), aqueous pump spray (—) 400 µg, and powder 800 µg (.....). Data have been normalised to metered doses with the pMDI formulation. (mean and s.e.mean).

administration were also in good agreement with previous data [11].

Relative to the metered dose the aqueous pump spray gave approximately 1.5 times higher % availability than

the powder administered with the nasal Turbuhaler® device. The latter in its turn gave 1.5 times higher % availability than the pMDI. However, the amount retained within the device was very small for the aqueous

Table 2 Pharmacokinetic parameters (arithmetic mean (s.d.)) in 16 healthy volunteers after nasal administration of budesonide from three different formulations. The systemic availability is given with reference to the metered dose (F_{metered}) and the dose-to-subject ($F_{\text{dose-to-subject}}$) (geometric mean 95% CI).

Formulation	C_{max} (nmol l ⁻¹)	t_{max} (h)	MAT (h)	F_{metered} (%)	$F_{\text{dose-to-subject}}$ (%)
pMDI	0.51 (0.30)	2.00 (0.33–4.15)‡	2.65 (0.75)	12.6 [10.5; 15.1]	21.0 [16.9; 25.9] [#]
Aqueous pump spray	0.99 (0.41)	0.63 (0.33–1.50)‡	1.57 (0.57)	29.0 [22.9; 36.7]	31.4 [23.8; 41.3]
Turbuhaler®	1.06 (0.58)	0.33 (0.17–0.75)‡	1.76 (0.54)	19.5 [16.4; 23.1]	40.8 [33.3; 49.8]

‡Median (range).

[#]The delivered dose was used instead of the dose-to-subject for the pMDI formulation.

pump spray as compared with the pMDI and Turbuhaler®. Relative to dose-to-subject, the systemic availability of the pMDI formulation was still only about 60% of the other two formulations. Difficulties in estimating the fraction of the dose that may have escaped the nose by backfiring through the pMDI canister may, however, have led to an underestimation of the drug loss and consequently the systemic availability with reference to the dose-to-subject for the pMDI formulation.

For the pMDI formulation, not only the extent of systemic absorption (F) of budesonide but also the plasma concentration profile, described by a lower $C_{\max}$, and a longer $t_{\max}$ and MAT differed from that of the other two formulations. A possible explanation for this is differences in deposition patterns in the nasal cavity; the pMDI formulation has been found to be deposited on a comparatively small area (Little's area) in the anterior one-third of the nasal cavity, with squamous and transitional non-ciliated epithelium and a relatively thick mucosal membrane [2, 12]. The other two formulations are deposited on a larger area including the turbinates [3, 4, 13]. The turbinates are covered by respiratory epithelium and are the primary sites for systemic absorption of nasally administered drugs [14]. The slow absorption of budesonide from the pMDI formulation, with a $t_{\max}$ of up to 4 h, is probably related to the slow clearance in the non-ciliated anterior part of the nose, a clearance which may last for several hours [15]. This can be compared with a mucociliary clearance half-life of about 10 min in the ciliated regions of the nose, as measured by the saccharine-dye test [16].

The results from the present investigation show that the systemic availability of the tested nasal formulations of budesonide differ. This may be related not only to differences in deposition patterns but also to differences in dissolution rate of the drug on the nasal mucosa, which in turn may be due to properties related to the compositions of the formulations. A glucocorticoid has to be absorbed into the target cells in the nasal mucosa in order to be able bind to the GCS receptor and exert its clinical effect. The absorption requires the drug to be dissolved, and almost all currently marketed nasal GCS are formulated as suspensions or dry powders. The dissolution rate of the drug particle on the nasal mucosa is thus critical and competes with the removal of drug by nasal mucociliary clearance. After local absorption into the nasal mucosa, the drug is systemically absorbed; as shown previously, the systemic availability of budesonide after nasal instillation of an experimental solution has been found to be complete, indicating that negligible biotransformation of budesonide takes place in the nose [5]. None of the currently marketed nasal GCSs has been shown to be inactivated locally in the nasal mucosa. Therefore, the systemic availability of a nasally adminis-

tered GCS should be a measure of the amount of drug that has been dissolved and subsequently absorbed by the nasal mucosa.

The systemic availability of nasally administered budesonide found in the present study is relatively high when compared with that of other nasal GCSs, i.e. fluticasone propionate (FP) and mometasone furoate (MF). A low systemic availability, which has been claimed for nasal FP (<2%) [17] and suggested for MF (<0.1%) [18], might be related to a rapid mucociliary clearance from the nasal mucosa as both drugs, due to a higher lipophilicity, can be assumed to have a poor solubility compared to budesonide on the nasal mucosa. The low figures of systemic availability claimed for FP and MF may also be related to difficulties in determining the systemic availability correctly due to plasma concentrations below the lower limit of quantification (LOQ). That plasma concentrations are below the lower LOQ does not exclude that the GCS is associated with a significant systemic activity [19]. For instance, a clinical dose of $200 \mu\text{g day}^{-1}$ of nasal FP was recently found to produce a significant suppression (43%) of overnight urinary cortisol [20], indicating a systemic absorption of FP. The systemic availability of MF after nasal administration remains to be investigated.

Nasal mucociliary clearance half-life has been observed to be slower in patients with allergic rhinitis (10.3 min) and non-allergic rhinitis (11.7 min) than in healthy controls (8.8 min) [16]. It is suggested that this difference is due to changes in the rheology of nasal mucus as a consequence of the underlying inflammatory process in rhinitis. However, the difference in mucociliary clearance between healthy subjects and rhinitis patients seems to be too small to affect the systemic absorption significantly. The influence of other factors associated with rhinitis on the systemic absorption of nasal GCS remains to be investigated.

In conclusion, the systemic availability of budesonide from three marketed nasal formulations was found to differ. The systemic uptake of budesonide was slower and less complete with the pressurized aerosol than with the aqueous pump spray and Turbuhaler®.

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