The influence of orally deposited budesonide on the systemic availability of budesonide after inhalation from a Turbuhaler®

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- 1 The aim of this pharmacokinetic study was to evaluate to what extent oropharyngeal deposition of drug contributes to the systemic availability of budesonide inhaled from a dry powder inhaler (Turbuhaler®).
- 2 The design was a randomized cross-over study in eight children aged 7–13 years. The plasma concentrations of the two epimers of budesonide (22R and 22S) after inhalation of 1 mg budesonide from a Turbuhaler were compared with the plasma concentrations obtained when the absorption of the drug deposited in the oropharynx was blocked by drinking and rinsing the mouth with charcoal before and after the inhalation.
- 3 The plasma concentrations of budesonide were significantly reduced by the charcoal treatment ($P < 0.01$) and the area under the time vs plasma concentration curve 0–4 h was significantly reduced from 9.5 to 8.0 mmol l⁻¹ h for 22S ($P < 0.01$) and from 7.6 to 5.7 mmol l⁻¹ h for 22R ($P < 0.01$).
- 4 The plasma concentrations and the AUCs after both Turbuhaler administrations were markedly higher than those obtained in earlier studies using other inhalers suggesting a higher intrapulmonary deposition of drug after Turbuhaler treatment.
- 5 It is concluded that oropharyngeal deposition of drug accounts for about 20% of the total systemic availability of budesonide inhaled from Turbuhaler. Thus, the main contribution to the system comes from budesonide absorbed in the airways.

Keywords budesonide systemic availability Turbuhaler inhalation

Introduction

Only about 10% of an aerosol dose delivered from a conventional metered dose inhaler (MDI) is deposited within the intrapulmonary airways [1–4]. The remaining part is deposited in the oropharynx or retained in the inhaler. From the oropharynx it is swallowed and subsequently absorbed. The systemic bioavailability of swallowed drug varies from 15–70% depending upon the glucocorticosteroid used [5–8]. The orally deposited drug has negligible clinical anti-asthma effect, but it does contribute to some extent to the systemic activity of the inhaled corticosteroid.

During recent years dry powder inhalers have become increasingly popular and when the freon ban becomes effective, these inhalers will be the only alternative for delivering inhaled glucocorticosteroids. However, the dry powder inhalers are associated with a higher oropharyngeal deposition of drug than spacers and hence a risk of higher systemic side effect.

Exactly how much the oropharyngeal drug deposition from a dry powder inhaler contributes to the systemic availability is not known. Therefore, the

present study was undertaken to elucidate to what extent the oropharyngeal deposition of drug contributes to the systemic availability of budesonide delivered from a dry powder inhaler (Turbuhaler) to children with asthma.

Methods

Four girls and four boys aged 7–13 years (mean = 10 years) were studied. Their weight was 25–54 kg (mean 42 kg) and their height 132–170 cm (mean 153 cm). The study was approved by the Ethics Committee of Northern Jutland, and informed consent was obtained from the children and their parents. Apart from having mild asthma the children were healthy according to physical examination and standard laboratory tests on blood and urine. On all study days pulmonary functions were higher than 75% of the predicted normal values.

The study was an open, randomized, cross-over trial comparing the systemic absorption of budesonide after

A) oral inhalation of 1.0 mg budesonide from a Turbuhaler with the systemic absorption of budesonide after

B) oral inhalation of 1.0 mg budesonide from a Turbuhaler under conditions that grossly prevented absorption of orally deposited drug.

The treatments were separated by 1–2 weeks and all children used the same Turbuhaler on the two study days. For each patient the Turbuhaler mouthpiece was replaced by a new unused one. To estimate the exact dose delivered to the subjects, all mouthpieces were analyzed with respect to budesonide deposition.

On day B oropharyngeal absorption was prevented as follows: just prior to treatment and immediately after it the children rinsed their mouth and gargled three times with a charcoal suspension (totally 5 g in 25 ml of water) that was subsequently swallowed. The same amount of charcoal suspension was swallowed 1 and 2 h after inhalation. This procedure has been shown to prevent absorption of oropharyngeally deposited budesonide [9].

The inhalations consisted of 5 doses of 0.2 mg budesonide. Each inhalation was performed as a rapid inhalation (inspiratory flow rate around 60 l min⁻¹) from functional residual capacity to total lung capacity. The Turbuhaler was always loaded in upright position.

The children refrained from inhaled glucocorticosteroids for the preceding 2 months, and at the time of the study none had received systemic treatment with steroids for at least 6 months. During the 48 h prior to the study, no oral intake of theophylline or β_2 -adrenoceptor agonists was allowed.

In order to eliminate contamination of blood samples, the administration of drug took place in a room well separated from the blood sampling station. Furthermore, during the inhalations the children and the assistant wore special protective coats and gloves, which were removed before blood sampling. The assistant administering the inhalations was not involved in the blood sampling procedures.

Blood was drawn from an indwelling catheter in a forearm vein. It was collected before and at 10, 20, 30, 40, 50 min and 1, 2 and 4 h after drug administration. To avoid contamination from the previous sample or dilution by the heparinized saline used to keep the

catheter open, the first 2 ml of blood in each sample was discarded. Normally, 3 ml of plasma is needed to assay budesonide. However, in order to reduce the loss of blood, smaller samples were taken 0, 10, 20, 30, 40 and 50 min after drug intake, and plasma was pooled to form an integrated sample from each subject. The integrated sample also included the 60 min value, which in addition was analyzed separately.

Each sample was analysed by a combined method of separation of the two budesonide epimers 22R and 22S by h.p.l.c., followed by r.i.a., and also by direct r.i.a. The direct r.i.a. is not specific for budesonide, but also to some extent detects its oxidized metabolites. The ratio of the direct r.i.a. value and the sum of the specifically measured epimers gives an indication of the metabolites present. However, because each epimer and each metabolite react with different sensitivity with the antibody the true amount of metabolites could not be calculated. The ratio is therefore useful as a qualitative measure of the amount of metabolites present.

The area under the curve of budesonide plasma concentration vs time (AUC) was estimated by the trapezoidal rule. In the pooling procedure the volume of each sample was represented in proportion to its contribution to the AUC: the 0 and 60 min sample volumes were only half those of the other samples. The analysis of the pool represents the average plasma concentration during the actual time period (0–60 min). The procedure is an accurate and blood-saving method for estimation of the AUC during the first hour, at the expense of detailed information about peak concentrations and the slope of the curve. The theoretical background for the pooling procedure has earlier been described [10].

Wilcoxon's rank sum test was used to compare the results from the two treatments.

Results

The mean plasma concentrations of the two budesonide epimers (h.p.l.c. + r.i.a. procedure) after the two treatments are shown in Figure 1. At all sampling times the plasma concentrations of epimer 22S were significantly

Figure 1 Plasma concentration curves 0–4 h of the two epimers of budesonide after inhalation of 1 mg budesonide from a Turbuhaler (●) and from a Turbuhaler when absorption of oropharyngeally deposited drug was prevented (■).

higher than those of epimer 22R ($P < 0.05$) after both administrations. Furthermore, for both epimers, the plasma concentrations after charcoal were significantly lower than the levels after the treatment without charcoal ($P < 0.01$).

The mean AUCs 0–4 h after the two treatments are given in Table 1. Since budesonide concentrations were low at 4 h, the 0–4 h AUCs express most of the AUCs up to infinite time and can therefore be regarded as a measure of systemic availability. It was then calculated that charcoal reduced the systemic availability of drug for both epimers, about 15% for 22S and 25% for 22R.

Analysis of the dose released from each Turbuhaler showed that the actual metered dose was 0.250 mg and not 0.200 mg per dose. The mean amount of budesonide recovered from the mouthpieces was 0.28 mg, thus giving, as a mean, 0.97 mg to the subjects.

One year earlier the same children had participated in another pharmacokinetic study of exactly the same design [11]. In that study 1 mg of budesonide was delivered from a Nebuhaler without simultaneous charcoal administration. The AUC 0–4 h for the two epimers after this treatment, with the difference in delivered dose adjusted for, have been added in Table 1 for comparison. For both epimers the systemic availability was markedly lower after Nebuhaler administration than after Turbuhaler + charcoal ($P < 0.001$). The ratios between the plasma concentration found by direct r.i.a. and those found by the combined method in the present study, the study with Nebuhaler [11] and after intravenous administration [12] are given in Table 2.

No side effects were reported.

Discussion

Budesonide can reach the systemic circulation by two different routes, by direct absorption through the mucosa in the airways, or by solvation in the saliva and subsequent swallowing and absorption from the gut. However, only the direct uptake in the airways, would circumvent the extensive first-pass metabolism of budesonide. If this pathway was the most important the amount of metabolites (described as the ratios of direct r.i.a. divided by h.p.l.c. + r.i.a.) would be expected to

be similar to those observed after intravenous administration. This was the case in the present study. The observed ratios were not of the 'oral type'. This confirms the conclusions from the AUC data, i.e., the vast majority of the systemically available drug comes from direct systemic absorption from the airways and the contribution from drug deposited in the mouth and pharynx is only in the order of 20%.

The clinical importance of the absorption of budesonide deposited in the mouth and pharynx is not known. However, high doses of orally ingested budesonide (4 and 8 mg) have been shown to have measurable effects on the cortisol excretion [6]. Therefore, it seems rational to recommend mouth-rinsing with water immediately after inhalation in patients treated with high doses of budesonide from a Turbuhaler. Such measures have recently been shown to remove about 80% of the drug deposited in the oropharynx and to decrease the systemic effects [13].

Earlier we performed two other pharmacokinetic studies with budesonide given via Nebuhaler to children [11, 12]. These studies showed very similar plasma concentrations and AUCs. Data from one of them are given in Table 1. The plasma concentrations and AUCs in the present study were markedly higher than those found in the earlier studies on the same patients. In the present study the vast majority of the systemically available drug on the charcoal day must have emanated from pulmonary absorption of drug deposited in the airways. A comparison between the AUCs after Turbuhaler with charcoal and Nebuhaler without charcoal (Table 1) indicated that the intra-bronchial deposition of budesonide was approximately twice as high after Turbuhaler treatment as after Nebuhaler treatment. Turbuhaler would therefore be expected to be clinically more effective than Nebuhaler. This is in agreement with the findings in some recent studies [14–17]. On the other hand Turbuhaler would also be expected to have a higher systemic activity than Nebuhaler. This has also been reported in one study [17]. A dose reduction should therefore be attempted when a patient is switched from Nebuhaler to Turbuhaler.

Conclusion

Orally deposited drug accounts for about 20% of the total systemic availability of budesonide inhaled from

Table 1 Area under the curve of the plasma concentration vs time 0–4 h for the two epimers of budesonide (mean $\pm$ s.d.) after inhalation of 1 mg budesonide from a Turbuhaler (A), from a Turbuhaler when absorption of oropharyngeally deposited drug was prevented and from a Nebuhaler (C). Nebuhaler data have been taken from an earlier study [11]

Treatment	AUC 0–4 h (nmol l ⁻¹ h)		
	Epimer 22S	Epimer 22R	
A Turbuhaler without charcoal	9.46 $\pm$ 1.58	7.63 $\pm$ 1.37	$P < 0.01$
B Turbuhaler with charcoal	8.04 $\pm$ 1.77	5.73 $\pm$ 1.13	$P < 0.01$
C Nebuhaler [11] without charcoal	4.62 $\pm$ 1.02	3.90 $\pm$ 0.94	

Table 2 Ratio of the total r.i.a. value and the specific r.i.a. value after h.p.l.c. separation for the 0–1 h integrated sample and the samples drawn at 1 and 2 h. Furthermore, the ratios obtained after oral and i.v. budesonide administration in earlier studies [11, 12] are included

	Ratio r.i.a./(h.p.l.c. + r.i.a.)		
	0–1 h	1 h	2 h
Oral [11]	2.65	2.88	2.82
Intravenous [12]	1.22	1.44	1.64
Turbuhaler	1.08	1.18	1.47
Turbuhaler + charcoal	1.15	1.26	1.28

Turbuhaler in asthmatic children. Inhalation via Turbuhaler seems to produce a higher deposition of drug in the airways than other inhalers. Further studies

are needed to compare the ratio of clinical effect/systemic effect for the various inhalers used for inhaled glucocorticosteroids.

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