Influence of Mouth Washing Procedures on the Removal of Drug Residues Following Inhalation of Corticosteroids

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Mouth washing after inhalation of corticosteroids is effective for prevention of local adverse effects such as hoarseness and oropharyngeal candidiasis. To establish an optimal procedure for such mouth washing, we investigated the removal rates of drug residues remaining on the oropharyngeal mucosa using various mouth washing methods following inhalation. A beclomethasone dipropionate metered dose inhaler (BDP-MDI) (100 μg) and a fluticasone propionate dry powder inhaler (FP-DPI) (100 μg) were used. The effects of different mouth washing methods were evaluated by quantification of drugs in the expectorated rinse solution using an HPLC method. The amounts of BDP recovered in the rinse after gargling and rinsing for 5 s each were 47.1 ± 13.6 μg, while they were 42.9 ± 9.4 μg after rinsing alone for 10 s and 38.7 ± 9.2 μg after gargling alone for 10 s. Under the same conditions, FP amounts were 32.9 ± 7.3 μg, 28.9 ± 2.4 μg, and 27.1 ± 7.9 μg, respectively. In a comparison of washing time, the amounts of BDP recovered were 49.8 ± 9.7 μg after gargling and rinsing for 2 s each, 53.5 ± 10.2 μg after those for 3 s each, and 47.1 ± 13.6 μg after those for 5 s each, while the amounts of FP under the same conditions were 36.4 ± 2.4 μg, 33.3 ± 6.4 μg, and 32.9 ± 7.4 μg, respectively. As for the effect of time lag before mouth washing, the amount of BDP recovered decreased by 65.7% with a lag time of 1 min and by 5.6% after 10 min, while that of FP decreased by 51.1% with a lag time of 1 min and by 7.7% after 10 min. Our results suggest that the amount of drugs removed by mouth washing is significantly associated with the time lag between inhalation and mouth washing. We concluded that immediate gargling and rinsing after inhalation is most useful for the removal of drugs following inhalation of corticosteroids.

Key words  inhaled corticosteroid; immediate mouth washing; mouth washing procedure; local adverse effect

Inhalation of corticosteroids is recognized as an important first line of anti-inflammatory defense therapy and the drugs have become primary agents in the treatment of asthma, though local adverse effects, such as hoarseness and oropharyngeal candidiasis, are often seen in patients treated with inhaled corticosteroids. Since the prevalence of candidiasis is positively correlated with increased dose and dosing frequency, it is considered that effective prevention against local adverse effects can be achieved by using a metered dose inhaler (MDI) with a spacer device, along with mouth washing after inhalation. Recently, we reported the effects of mouth washing on removal of drug residues after use of a beclomethasone dipropionate (BDP)-MDI and fluticasone propionate (FP) dry powder inhaler (FP-DPI). However, development of candidiasis has been reported even in patients who washed their mouth after inhalation, which is likely caused by residual corticosteroids from insufficient mouth washing. In the present study, we investigated the influence of different methods of mouth washing on the removal rates of inhaled corticosteroids after using a BDP-MDI and FP-DPI.

MATERIALS AND METHODS

Five healthy volunteers, (4 males, 1 female; mean age 34.2 ± 8.7 years old, range 26—45 years) participated in this study. Patients with asthma that use inhaled corticosteroids range widely in age from children to adults, and local adverse effects from inhaled corticosteroids are common findings in all ages. Thus, the age range of the present patients was considered to be appropriate. The objectives and protocol were fully explained to each, and signed informed consent was obtained from all subjects prior to beginning the study.

For the inhaled corticosteroids, we used Becotide®100 (GlaxoSmithKline K.K.) as the type of BDP, which was administered by use of an MDI, and Flutide®100 Rotadisk® (GlaxoSmithKline K.K.) as the type of FP, which was administered by use of a DPI via a Diskhaler. In order to limit variations in the amounts of inhaled drugs between individuals, we utilized the following procedures. First, we placed the BDP-MDI in the mouth and instructed the subject to close their mouth around it, after which the examiner depressed the top of the inhaler once. Following that single spray, the subject was instructed to hold their breath for 15 s, after which each washed their mouth with water according to the enclosed Information Leaflet. It is known that drug residue remains in the Diskhaler following a single inhalation, therefore, administration was repeated 3 times per medicine blister to minimize the amount of drug residue in the device. All subjects were trained to perform the correct procedure of inhalation and mouth washing several times before the experiment. Further, the subjects read again the enclosed Information Leaflet just prior to inhalation under observation. For each drug, mouth washing, mouth washing duration, and lag time from inhalation until mouth washing were performed in that order. Each examination was separated by 2 to 3 d, with the experiments with FP-DPI performed first, followed by those with BDP-MDI. We confirmed that no drug residues remained in the mouth for at least 1 d at preliminary examinations done before each experiment. The effects of the various methods of mouth washing were investigated using FP-DPI and BDP-MDI performed first, followed by those with BDP-MDI.
on the removal of drug residues from the mouth were evaluated by quantification of each drug in the expectorated mouth washing rinse after inhalation, using a high-performance liquid chromatographic method reported previously.\(^7\)\(^8\)

Statistical differences in the amount of recovered drug among the methods and mouth washing duration periods were evaluated by analysis of variance (ANOVA). The relationship between the amount of recovered drug and lag time from inhalation until mouth washing was compared statistically used a two-sided t test. All data were analyzed using the Statcel software package (OMS Publishing Inc., Japan). Statistical tests were two-tailed with the level of significance set at 5%.

Mouth Washing Methods for Removal of Drug Residues Three kinds of mouth washing methods were used; gargling and then rinsing the mouth with water for 5 s each, rinsing only for 10 s, and gargling only for 10 s. The total volume of water used for mouth washing was 100 ml, which was divided into 5 aliquots of 20 ml. In a single trial, the mouth washing method was repeated 5 times, with each rinse collected for examination. Previous studies have found that the amount of drugs recovered by mouth washing (gargling for 5 s and rinsing for 5 s) 3 times was approximately 95% of that recovered by mouth washing 5 times.\(^7\)\(^8\) Nevertheless, in the present study, mouth washing was repeated 5 times, because we considered that 95% of the drug may not be removed by mouth washing only 3 times with the procedures employed.

Mouth Washing Duration for Removal of Drug Residues The duration of mouth washing was investigated by gargling and rinsing for 2, 3, or 5 s, using the same sampling method as noted above.

**Lag Time from Inhalation until Mouth Washing** Lag times of 0, 1, 2.5, 5, and 10 min between inhalation and mouth washing were investigated. For mouth washing, the subjects were asked to gargle and then rinse for 5 s each. The total volume of water for mouth washing was 60 ml, which was divided into 3 aliquots of 20 ml. In this experiment, mouth washing was repeated 3 times in a single trial, as previous studies have found that the amount of drugs recovered by mouth washing 3 times was approximately 95% of that recovered by mouth washing 5 times.\(^7\)\(^8\)

**RESULTS**

Influence of Mouth Washing Procedures on Removal of Drug Residues Figure 1 shows the amounts of drugs recovered after performance of the 3 methods of mouth washing following use of the BDP-MDI and FP-DPI. In the case of the BDP-MDI, the most effective method for mouth washing was gargling and rinsing for 5 s each (recovered amount, 47.1±13.6 μg), followed by rinsing only (42.9±9.4 μg) and gargling only (38.7±9.2 μg), with a similar trend observed when using the FP-DPI (32.9±7.3 μg, 28.9±2.4 μg, and 27.1±7.9 μg, respectively). No significant differences were observed among these methods.

Influence of Duration of Mouth Washing on Removal of Drug Residues Figure 2 shows the amounts of drugs recovered following gargling and rinsing for 2, 3, or 5 s following use of the BDP-MDI and FP-DPI. With the BDP-MDI, the amounts recovered were 49.8±9.7 μg after gargling and rinsing for 2 s, 53.5±10.2 μg after 3 s, and 47.1±13.6 μg after 5 s, while those were 36.4±2.4 μg, 33.3±6.4 μg, and 32.9±7.4 μg, respectively, with the FP-DPI. No significant differences were observed among the durations of mouth washing with both inhalation methods.

Influence of Lag Time from Inhalation until Mouth Washing on the Removal of Drug Residues Figure 3 shows the relationships between lag time from inhalation until mouth washing on the amounts of drugs recovered. The relative amounts of drugs were decreased by 65.7±17.0%...
after 1 min and by 5.6±6.0% after 10 min, as compared to immediately following inhalation (0 min) in the case of BDP-MDI, and by 51.1±16.3% after 1 min and 7.7±2.2% after 10 min in the case of FP-DPI.

DISCUSSION

Local adverse effects such as oropharyngeal candidiasis and hoarseness are often seen in patients following treatment with inhaled corticosteroids. Previous studies have found that local adverse effects such as candidiasis were related to increased doses of corticosteroids. As a precaution, it is recommended that mouth washing after inhalation be performed, however, there is no known report of a comparison of the effectiveness of different mouth washing methods. In the present study, we investigated the effects of removal of drug residues using various methods of mouth washing.

No significant differences were observed regarding the technique used for removal of drug residues between the 3 methods of mouth washing (gargling and rinsing, rinsing only, gargling only) following corticosteroids inhalation, though gargling and rinsing tended to remove a greater quantity, followed in order by rinsing only and gargling only. We speculated that these results were due to the fact that the contact interface between the water used for rinsing and the mucous membrane in the mouth is large, thus the combination of gargling and rinsing was most effective for the removal of drug residues, as compared with either alone. Our results also suggested that the duration of mouth washing did not have a significant influence on the amount of removed drug residues.

In contrast, the amount of drugs removed by mouth washing was affected by the lag time between inhalation and washing, thus immediate gargling and rinsing after inhalation is considered to be the most effective. The amount of drugs recovered after a lag time of 1 min was 15.4±12.8% less than when mouth washing was performed immediately following inhalation, which we considered was due to their removal by saliva. We previously reported that saliva kept in the mouth for 1 min, after spraying 50 μg of FP, was kept in the mouth for 1 min after spraying 50 μg of FP-DPI, and by 51.1±16.3% after 1 min and 7.7±2.2% after 10 min in the case of FP-DPI.

The mechanisms by which inhaled and topically applied steroids have effects on oral candidiasis have not been fully clarified. In the case of inhaled administration, the lesions are generally localized in areas where the aerosol is deposited, and the degree of candidiasis is probably related to dosage and frequency of therapy. We previously reported findings for a patient who washed their mouth with a lag time of 15 min after inhalation and developed oral candidiasis. For the prevention of dysphonia, mouth washing immediately after inhaling the drug is recommended to minimize local absorption. Further, it is considered that local adverse effects occur with frequent administrations of inhaled corticosteroids at a high dose, even when the treatment period is short. Thus, immediate mouth washing after inhalation should be useful for reducing local adverse effects. On the other hand, oropharyngeal absorption of FP was found to not significantly contribute to its overall systemic bioactivity, as assessed by sensitive measures of adrenal suppression. In addition, direct oral mucosal absorption of an inhaled steroid does not have an important contribution to systemic bioavailability. As a result, there is no reason to employ mouth washing to reduce its systemic effects, though it may be of value for reducing the incidence of oral candidiasis.

Together, these findings suggest that if mouth washing is not performed immediately after inhalation, drug residues will be swallowed into the throat along with saliva. Therefore, we recommend immediate gargling and rinsing following inhalation of corticosteroids for the prevention of local adverse effects.

REFERENCES
