Kinetic Analysis of Effects of Mouth Washing on Removal of Drug Residues Following Inhalation of Fluticasone Propionate Dry Powder

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Fluticasone propionate dry powder inhaler (FP-DPI) is widely used for the treatment of asthma. However, local adverse effects such as oropharyngeal candidiasis are often seen and mouth washing after inhaling is recommended. In our previous study, we reported a nonlinear relationship between the amount of drug residue and number of times mouth washing was employed. Thus, we developed a compartment model, in which the inhaled drugs were distributed in both easy and difficult to remove areas. Using this model, we analyzed drug removal efficiency in each area with different mouth washing procedures. Three methods of mouth washing were studied; gargling and rinsing in combination, rinsing alone, and gargling alone, following administration of FP-DPI by sprinkling or inhaling. The amounts of drugs recovered from areas considered to be easy to remove (X1) and difficult to remove (X2) were determined using a nonlinear least-squares program, while the removal efficiency of each of the 3 methods was also calculated. The ratios of X1 after sprinkling and inhalation were 63.9% and 21.8%, respectively, while those of X2 were 6.0% and 12.4%, respectively. The numbers of mouth washings required to remove half doses from easy and difficult to remove areas were 0.2 and 1.4 times, respectively, with a combination of gargling and rinsing following inhalation of FP-DPI, while those were 0.3 and 3.6 times, respectively, with rinsing alone, and 0.4 and 5.8 times, respectively, with gargling only, thus demonstrating significant differences among the mouth washing methods for efficiency in the difficult to remove area. The present results show that the employed methods of mouth washing had a significant influence on the removal of drug residues following inhalation of FP-DPI, with gargling and rinsing in combination considered to be the most effective.

Key words mouth washing; fluticasone propionate; dry powder inhaler; compartment model; local adverse effect

Inhaled corticosteroids are widely used for treatment of asthma, though local adverse effects, such as candidiasis and hoarseness, are often seen in patients treated with those drugs. Therefore, the Packaging Inserts enclosed with such medications recommend mouth washing after inhalation for prevention of local adverse effects. In spite of that recommendation, candidiasis has been reported by patients who washed their mouth after inhalation. Therefore, we carried out a series of studies to investigate the influence of different methods of mouth washing on the removal rates of inhaled corticosteroids. More than 90% of the drug was recovered by rinsing alone or gargling alone, 50% by rinsing twice, and less than 30% by gargling alone. In our previous study, we reported a nonlinear relationship between the amount of drug residue and the number of times mouth washing was employed. Further, k1 and k2 represent the constants of removal efficiency of X1 and X2, respectively.

The amount removed (Xr) by each method of mouth washing was expressed by the following equation:

\[ X_r = X_n \cdot F \cdot T \cdot \exp(-k \cdot n) \]  

In the present study, we investigated the differences in removal efficiency of drug residues from both easy and difficult to remove areas using 3 different methods of mouth washing: gargling and rinsing in combination, rinsing alone, and gargling alone, using a compartment model.

MATERIALS AND METHODS

Compartment Model for Analysis of Removal Efficiency of Drug Residues by Mouth Washing Flutide® (FP-DPI) 50, 100, and 200 Rotadisk® dosages were used in the present study. In addition, we employed our previously reported experimental data in the analysis, in which 3 healthy volunteers (2 males, 1 female; mean age 38.3 ± 9.3 years old, range 28—45 years) participated. In the present experiment, mouth washing was started immediately following sprinkling directly in the mouth or inhalation of 1 blister, and consisted of gargling and rinsing with water for 5 s each, then the procedures were repeated 5 times. The total volume of water used for each mouth washing was 100 ml, which was divided into 5 aliquots of 20 ml each. We also developed a compartment model, in which inhaled FP-DPI residue was distributed into 2 different areas, one from which the drug was easily removed and the other from which it was difficult to remove by mouth washing. The equations used for the model were as follows:

\[ X_1 = X_n \cdot F \cdot (1 - T) \cdot \exp(-k_1 \cdot n) \]  

\[ X_2 = X_n \cdot F \cdot T \cdot \exp(-k_2 \cdot n) \]
with a level of significance set at 1%.

Statistical tests were two-tailed with Bonferroni correction.

Washing Procedures

Analytical procedure used as noted above.

vice were collected using 20 ml of water, with the same ana-

was injected into a chromatograph. Drug residues in the de-


45 years) participated in that previous study.

(4 males, 1 female; mean age 34.2


RESULTS

Compartment Model for Analysis of Removal Efficiency of Drug Residues by Mouth Washing

Figure 1 shows fitted curves for the amount of FP in water collected after gargling and rinsing following sprinkling or inhalation of 50, 100, or 200 μg of FP-DPI. Here, it was assumed that \( k_1 \) and \( k_2 \) represented the same values following sprinkling and inhaling with the same mouth washing procedure. The method of sprinkling was sprinkling dry powder into the mouth after opening the upper part of 1 blister with a cutter. Inhalation was not performed after sprinkling.

Sample Collection and Measurement of FP

Quantification of FP was carried out using a high performance liquid chromatographic method. Twenty milliliters of mouth washing sample was added to 5 ml of chloroform containing trans-stilbene (0.1 mg) as an internal standard, and the mixture was shaken and centrifuged, after which the aqueous phase was extracted. The lower organic phase of 3 ml was then transferred to a clean conical tube and evaporated. The residue was dissolved in 1 ml in the mobile phase and 20 μl was injected into a chromatograph. Drug residues in the device were collected using 20 ml of water, with the same analytical procedure used as noted above.

Analysis of Removal Efficiency by Different Mouth Washing Procedures

In order to estimate \( k_1 \) and \( k_2 \), previously obtained data for the amount of FP in water collected after gargling and rinsing for 5 s each, rinsing alone for 10 s, and gargling alone for 10 s, each repeated 5 times, after inhalation of 100 μg of FP-DPI were fitted to Eq. 3 using a nonlinear least-squares program for comparisons among different mouth washing procedures. Five healthy volunteers (4 males, 1 female; mean age 34.2 ± 8.7 years old, range 26—45 years) participated in that previous study. \( F \) and \( T \) were substituted for the estimated \( k_1 \) and \( k_2 \) values are shown in Table 1. The fitted curves were well matched to the values obtained in the experiments. The estimates \( F \) and \( T \) values are shown in Table 1. In addition, the values of \( k_1 \) and \( k_2 \) were estimated to be 2.48 and 0.51 (times\(^{-1}\)), respectively. The percentage of doses in easily removed (\( X_1 \)) and difficult to remove (\( X_2 \)) areas were calculated to be 63.9% and 6.0%, respectively, after sprinkling, and 21.8% and 12.4%, respectively, after inhalation.

Analysis of Removal Efficiency of Different Mouth Washing Procedures

Figure 2 shows fitted curves for the amount of FP in water collected after gargling and rinsing following sprinkling or inhalation of 50, 100, or 200 μg of Fluticasone Propionate Dry Powder.

### Table 1. Estimated Parameters for Removal of Drug Residue by Mouth Washing after Sprinkling or Inhalation of 50, 100, or 200 μg of Fluticasone Propionate Dry Powder

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sprinkling</th>
<th>Inhalation</th>
</tr>
</thead>
<tbody>
<tr>
<td>( F )</td>
<td>0.70±0.02</td>
<td>0.34±0.04</td>
</tr>
<tr>
<td>( T )</td>
<td>0.09±0.15</td>
<td>0.36±0.22</td>
</tr>
</tbody>
</table>

Estimated value±S.E.

\[
X_1 = X_0^F - (X_1 + X_2) = X_0^F - 1 - T \cdot \exp(-k_1 \cdot n) - T \cdot \exp(-k_2 \cdot n)
\]  

(3)
the obtained $F$, $T$, $k_1$, and $k_2$ values, with the results summarized in Fig. 3. The estimated numbers of mouth washing that removed half doses from easily removed and difficult to remove areas following inhalation of 100 $\mu$g of Fluticasone Propionate Dry Powder were 0.2 and 1.4 times, respectively, by gargling and rinsing for 5 s each, while those for rinsing alone were 0.3 and 3.6 times, respectively, and gargling alone were 0.4 and 5.8 times, respectively (Table 3). Consequently, mouth washing after inhalation of FP-DPI was most effective with gargling and rinsing in combination, followed in order by rinsing alone and gargling alone. Notably, the removal efficiency represented by $X_2$ was clearly superior with gargling and rinsing in combination.

**DISCUSSION**

It has been suggested that mouth washing following inhalation of corticosteroids can prevent local adverse effects such as candidiasis and hoarseness. We previously confirmed that mouth washing after inhalation is effective for removal of drug residues. However, the removal of drug residues by mouth washing and number of times required were different between easily removed and difficult to remove areas, thus we constructed a compartment model and conducted analyses with it. The relationships between the ratio of amount of drugs remaining after mouth washing and removal efficiency were analyzed with different methods using experimental data and a nonlinear least-squares program.

The amount of sprinkled FP removed by mouth washing was 69.9%, while the amount of inhaled FP-DPI was 34.2%. Since the amount of drug remaining in the device was shown to be 8.8±4.3%, we considered that approximately 30% of the dose was positioned in other areas of the mouth (pharynx and lung, as well as others) following inhalation. The ratio of $X_1$ to total dose was 63.9% after application of sprinkled FP in the mouth and 21.8% after inhalation, while those ratios of $X_2$ to total dose were 6.0% and 12.4%, respectively. Thus, the ratio of medication that remained in the difficult to remove area was significantly greater with inhalation as compared to administration by sprinkling.

The $k_1$ values were 2.90±0.48 (times$^{-1}$) with gargling and rinsing for 5 s each, 2.82±0.37 (times$^{-1}$) with rinsing alone, and 1.85±0.14 (times$^{-1}$) with gargling alone with inhaled FP-DPI. Further, the $k_2$ values with those were 0.49±0.03 (times$^{-1}$), 0.20±0.01 (times$^{-1}$), and 0.12±0.01 (times$^{-1}$), respectively. As compared to the easily removed area, the differences among the different mouth washing procedures for

**Table 2. Estimated Parameters for Removal of Drug Residues Using 3 Methods of Mouth Washing Following Inhalation of 100 $\mu$g of Fluticasone Propionate Dry Powder**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Gargling and rinsing</th>
<th>Rinsing alone</th>
<th>Gargling alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_1$ (times$^{-1}$)</td>
<td>2.90±0.48 (a)</td>
<td>2.82±0.37 (b)</td>
<td>1.85±0.14 (c)</td>
</tr>
<tr>
<td>$k_2$ (times$^{-1}$)</td>
<td>0.49±0.03 (a)</td>
<td>0.20±0.01 (b)</td>
<td>0.12±0.01 (c)</td>
</tr>
</tbody>
</table>

Estimated value±S.E. Significant differences ($p<0.01$) were determined using a two-tailed multiple t-test with Bonferroni correction (3 comparisons between 3 groups): a) gargling and rinsing vs. rinsing; b) gargling and rinsing vs. gargling; c) rinsing vs. gargling.

**Table 3. Estimated Number of Mouth Washings Required to Remove Half Doses from $X_1$ and $X_2$ Following Inhalation of FP-DPI***

<table>
<thead>
<tr>
<th>Method</th>
<th>$X_1$</th>
<th>$X_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gargling and rinsing</td>
<td>0.2</td>
<td>1.4</td>
</tr>
<tr>
<td>Rinsing alone</td>
<td>0.3</td>
<td>3.6</td>
</tr>
<tr>
<td>Gargling alone</td>
<td>0.4</td>
<td>5.8</td>
</tr>
</tbody>
</table>
the difficult to remove area were large.

We speculated that the difficult to remove area was located in the region from the mouth to the pharynx, and consider that there is an indistinct relationship between the incidence of candidiasis and drug residue in the region of the pharynx, because there is no report of that condition occurring in the oropharynx. The mouth washing procedure utilized seems to be important, as candidiasis has been reported by patients who washed their mouth after inhalation. In our previous study, mouth washing with water removed residual drugs in the mouth. However, water might not reach around the pharynx easily, depending on the mouth washing procedure employed. The pharynx curves between the oral cavity and esophagus, and dry powder could easily adhere to the curved portion. Thus, we speculated that the difficult to remove area is distributed in the region from the oral cavity to the pharynx.

The numbers of times of mouth washing required to remove a half dose from the easily removed area were calculated to be 0.2 by gargling and rinsing in combination, 0.3 by rinsing alone, and 0.4 by gargling alone, and each was shown able to remove 80% or more of the drug residue by washing once. In contrast, the numbers of times for the difficult to remove area were 1.4 by gargling and rinsing in combination, 3.6 by rinsing alone, and 5.8 by gargling alone, which demonstrated larger differences among the methods as compared to the easily removed area. When the mouth washing methods were repeated 5 times, the removal ratios from the difficult to remove area were 11.4% with gargling and rinsing (91.9% with \( X_1 \) assumed to be 100%), 7.7% with rinsing alone (62.1% with \( X_2 \) assumed to be 100%), and 5.6% with gargling alone (45.2% with \( X_2 \) assumed to be 100%).

We found that gargling and rinsing in combination was most effective, especially with the difficult to remove area, as more than 90% of the drug was recovered as compared to the total amount of drug removed by mouth washing. Further, in the easily removed area, mouth washing performed twice removed more than 90% of the drug, while 5 times was required to remove the same amount from the difficult to remove area. These results suggest that the method of mouth washing employed has a relationship to local adverse effects.

The mechanisms responsible for the development of oral candidiasis by topically applied steroids have not been fully clarified. The lesions involved are generally localized in areas where aerosol is deposited, and the degree of candidiasis is probably related to dosage and frequency of therapy. Candidiasis overgrowth is usually due to inhibition of normal host defenses by local corticosteroid administration. Candidiasis can be seen in the oral mucosa where inhaled corticosteroids are likely to have contacted, which has been suggested to be a consequence of immunosuppression on the oral mucosal surface. In three cases of esophageal candidiasis rated as Grade 3, the symptoms disappeared in two and decreased to Grade 1 in one by simply changing the FP-DPI inhalation administration periods to before breakfast and before dinner. That study concluded that FP remaining in the esophagus was removed by the passage of food. Based on those results, we considered that there is a similar relationship in cases of esophageal candidiasis between FP remaining in the oral cavity after mouth washing and local adverse effects.

Our results showed that drug removal efficiency was decreased in order of gargling and rinsing in combination, rinsing alone, and gargling alone, which might be related to the local adverse effects often seen with the use of inhalation corticosteroids in spite of mouth washing. We concluded that gargling and rinsing in combination was the most effective method of mouth washing following inhalation of fluticasone propionate dry powder, especially for the purpose of removing drugs from difficult to remove areas.

REFERENCES