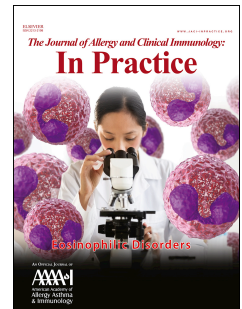


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Residual Fluticasone in the Oral Cavity after Inhalation with Different Tongue Positions

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Clinical Implications

The residual amount of fluticasone in the oral cavity was compared between 2 different tongue positions during inhalation. This study verified that lowering the tongue during inhalant uptake allows less inhaled medication to be retained in the mouth and presumably a larger amount of inhalant to be delivered into the trachea.

To the Editor:

Inhalants are the basis of bronchial asthma treatment, and these drugs are ineffective unless they are efficiently delivered past the trachea into the bronchial tree. Although correct inhaler use is emphasized in inhalation instructions, no studies have been conducted on the intraoral conditions during inhalation. We hypothesized that if the tongue is not intentionally lowered during inhalation, some amount of inhalants might be trapped on the tongue.

In our first study, we filmed intraoral conditions with an endoscope in 6 healthy volunteers to examine how different tongue positions affect the flow of placebo powder/particles. We reported a significantly larger amount of placebo powder/particles reached the pharynx and flowed toward the trachea for both fluticasone furoate/vilanterol (Relvar[®]) and fluticasone propionate/formoterol fumarate (Flutiform[®]) practice inhalers when the tongue was lowered than when it was not.¹

In our second study, we made a paper tube of the same size and shape as the mouthpiece of a pressurized metered-dose inhaler (pMDI, Flutiform), fixed an endoscope at the center of the paper tube with tape, and filmed the intraoral conditions in 9 healthy volunteers with and without tongue lowering from the actual position where the inhalants are ejected. In all volunteers, the percentages of the visible posterior pharyngeal wall area were significantly higher when the tongue was lowered than when it was not. Our second study verified that lowering the tongue keeps the inflow route to the trachea for inhalants wide open.² These 2 studies suggested that inhalants are more efficiently delivered into the trachea when the tongue is lowered during inhalation.

We conducted this third study to further verify our findings in patients with bronchial asthma. Patients inhaled the same dose of fluticasone with and without lowering the tongue. After each inhalation, they gargled water 3 times and the amount of residual fluticasone collected in gargling water was compared. We considered that a smaller amount of fluticasone

trapped in the oral cavity indicated a larger amount of the drug delivered into the trachea.

The present study was approved by the Medical Research Ethics Committee of Fujita Health University (HM17-094). The subjects comprised 43 patients with bronchial asthma receiving outpatient treatment at our hospital (20 men, 23 women; mean age, 53.5 ± 21 years). The long-term management drugs were salmeterol/fluticasone propionate (Adoair Diskus[®]; 250 μ g, dry powder inhaler [DPI]) in 19 subjects and Flutiform (125 μ g; pMDI) in 24 subjects.

At outpatient visits, the subjects performed regular morning inhalation (1 inhalation of Adoair Diskus [250 μ g] or 2 inhalations of Flutiform [125 μ g]) and then gargled water 3 times: the men with 20 mL water each time (total 60 mL) and the women with 15 mL water each time (total 45 mL). All gargling water was collected. For the first collection, the subjects inhaled the drugs as usual without paying any attention to the tongue position (without lowering the tongue) and then gargled water (Figure 1(a)). After the gargling water was collected, the subjects were instructed to place their tongue under the tip of the mouthpiece, to lower the tongue and its root as if to pronounce “HO,” and to inhale the drugs with the pharynx kept expanded (Figure 1(b)). They were also instructed to keep lowering their tongue during drug inhalation at home.

At the following outpatient visit, the subjects inhaled the morning dose of the inhalants with the tongue lowered, and gargling water was collected in the same manner. The collected gargling water was stirred, and 10 mL of it was frozen and stored at -20°C . Then, fluticasone concentrations were measured using liquid chromatography/tandem mass spectrometry. The specimens were processed through protein precipitation with acetonitrile/methanol (1:1, v/v). The measured fluticasone concentrations were converted to the residual amount in consideration of the different amount of gargling water used by male and female subjects. All results are expressed as mean $\pm$ standard deviation. Statistical analysis was performed using

t-test, and $P < 0.05$ was considered to indicate a significant difference.

After inhalation of Adair Diskus (250 μg), the amount of residual fluticasone in gargling water was significantly smaller when the tongue was lowered ($109.3 \pm 40.6 \mu\text{g}$) than when it was not ($144.9 \pm 54.0 \mu\text{g}$) ($P = 0.0156$) (Figure 2(a)). After inhalation of Flutiform (250 μg), the residual amount was significantly smaller when the tongue was lowered ($62.3 \pm 37.2 \mu\text{g}$) than when it was not ($138.8 \pm 61.3 \mu\text{g}$) ($P < 0.001$) (Figure 2(b)).

The guidelines from the National Asthma Education and Prevention Program³ and the Global Initiative for Asthma⁴ indicate that the basis of bronchial asthma treatment is inhalation of corticosteroids, and that regular inhalation therapy is essential. Various studies worldwide have promoted correct inhaler use.⁵⁻⁷ Although correct inhaler use is essential, no clinical studies have been conducted on the delivery of inhaled drugs from the mouthpiece to the trachea. In our first and second studies, we suggested that inhalants could be more efficiently delivered into the trachea by lowering the tongue during inhalation. To further verify our assumption, we measured the amount of residual fluticasone in the oral cavity after inhalation in patients with bronchial asthma who regularly inhale fluticasone. We considered that a smaller residual amount in the oral cavity indicates a larger amount delivered into the trachea. Our results showed that the amount of residual fluticasone in the oral cavity was significantly smaller when the tongue was lowered while inhaling both DPI and pMDI. Therefore, we conclude that lowering the tongue during inhalation reduces the amount of inhalants trapped on the tongue so that a larger volume of inhalants can be delivered into the trachea.

These 3 studies suggested that lowering the tongue during inhalation reduces the amount of inhalants trapped on the tongue so that the drugs can be efficiently delivered into the trachea. Notably, this technique can not only be applied for all inhalants in patients with mild to severe bronchial asthma, but also does not incur additional costs. In recent years, articles on

cost-effectiveness have also been published.^{8,9)} We now plan to study the clinical effects of this technique in patients with bronchial asthma.

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Figure Legends

Figure 1. Tongue positions during inhalation. The tip of a bronchoscope was placed 5 mm from the first incisor while filming. The visible posterior pharyngeal wall during inhalation is demarcated with a light blue line. The posterior pharyngeal wall area was measured from the images using a hypothetical 10-cm long and 10-cm wide region.

(a) Picture of the oral cavity with the tongue not lowered. The inflow route from the pharynx to the trachea is narrow (posterior pharyngeal wall area: 1.1 cm²).

(b) Picture of the oral cavity when the tongue is placed under the inferior end of the inhaler and lowered. The inflow route from the pharynx to the trachea is kept wide open (posterior pharyngeal wall area: 7.0 cm²).

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Figure 2

(a). Volume of residual fluticasone in gargling water after inhalation of Adoair Diskus (250 µg). The volume was significantly smaller when the tongue was lowered (right) than when it was not (left) ($P = 0.0156$).

(b). Volume of residual fluticasone in gargling water after inhalation of Flutiform (250 µg). The volume was significantly smaller when the tongue was lowered (right) than when it was not (left) ($P < 0.001$).

