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ORIGINAL ARTICLE

Superiority of Nebulized Corticosteroids over Dry Powder Inhalers in Certain Patients with Cough Variant Asthma or Cough-Predominant Asthma

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ABSTRACT

Background: The particle distribution might differ between nebulizer therapy and metered-dose inhaler (MDI) or dry powder inhaler (DPI) therapy because the particles repeatedly enter/re-enter the airways with the nebulizer. Inhaled corticosteroids (ICS) were administered with a nebulizer to assess the benefit of changes in the distribution of particles in patients with cough variant asthma (CVA) and cough-predominant asthma (CPA).

Methods: Patients whose symptoms were not controlled by their current therapy were enrolled. In patients receiving high-dose ICS by MDI or DPI (ICS-MDI/DPI), steroid therapy was switched to 1,320 μg/day of nebulized dexamethasone (1,600 μg as dexamethasone sodium phosphate) (chronic steroid-independent group). In patients receiving systemic steroids regardless of their ICS-MDI/DPI therapy, nebulized dexamethasone was added and any concurrent ICS-MDI/DPI therapy was halted to detect a steroid-sparing effect (chronic steroid-dependent group). In patients with acute exacerbation of CVA or CPA and persistent symptoms despite systemic corticosteroids, nebulized dexamethasone was added to assess its effect (acute group).

Results: Superior symptom control was achieved in 10 out of 12 steroid-independent patients, 3 out of 6 steroid-dependent patients, and all 7 acute patients.

Conclusions: Delivery of ICS via a nebulizer has advantages over ICS-MDI/DPI in some patients with CVA or CPA.

KEY WORDS

budesonide, cough, dexamethasone, nebulizer, trachea

INTRODUCTION

Inhaled corticosteroids (ICS) are the most effective long-term therapy for the prevention of asthma, including cough variant asthma (CVA) and cough predominant asthma (CPA). Deposition of inhaled aerosols is mediated by the processes of impaction, sedimentation, diffusion, and turbulent diffusion. Particles larger than 3 μm are mainly deposited through impaction, while the smaller ones are carried in the air current due to friction and are deposited in the peripheral airways by other mechanisms.[1] In the oropharynx and the central bronchi, impaction is the mechanism responsible for particle deposition.[2,3] Experiments involving a single inhalation in a model of the trachea and bronchi have revealed that the deposition of particles in the central airways is not uniform,[3-7] with bifurcations being the sites of heavy deposition.[1,3,5] However, deposition of particles by a nebulizer has never been investigated and the pattern

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of particles distribution obtained with a nebulizer is likely to be different from that achieved with currently available devices, such as the metered-dose inhaler (MDI) or dry powder inhaler (DPI), because particles enter and re-enter the airways repeatedly and fill the entire lumen during all phases of the respiratory cycle. There are also other differences such as slower inspiration and humidification of the inspired air.

Cough receptors are distributed widely throughout the airways from the pharynx to the bronchi[8,9] and tracheitis is known to exist in patients who have diseases for which the cough is a leading symptom,[10] and low particle deposition on the tracheal mucosa might contribute to persistent cough despite ICS therapy. We hypothesized that delivery of ICS by using nebulizer might have a different effect compared to single-inhalation methods such as MDI or DPI due to a change of the particle deposition pattern, especially in the central airways including the trachea. Therefore, we employed nebulizer ICS therapy to treat patients with CVA or CPA who had persistent symptoms resistant to therapy including single-inhalation ICS. The present retrospective case series study was performed to analyze the efficacy of nebulizer ICS therapy.

METHODS

The participants in this study consisted of CVA or CPA patients whose symptoms was not adequately controlled by their current therapy, including high-dose ICS delivered by MDI or DPI [(ICS-MDI/DPI) 800 μg/day of budesonide (BUD, Pulmicort Turbuhaler®) or fluticasone propionate (FP, Flutide Diskus®)], and who were treated at the Pulmonology Department of the International Medical Center of Japan from December 2002 to July 2006 or at the Pulmonology Department of the National Hospital Organization Disaster Medical Center from December 2004 to July 2006. CVA was defined as continuous cough for more than 3 weeks with no observed symptomatic or audible wheezing on auscultation that responded to inhalation of β2-stimulants, based on the simplified diagnostic criteria for CVA.[11] CPA was defined as chronic cough with minimal symptoms of wheezing.[12] In patients who were not being treated with systemic steroids (chronic steroid-independent group), ICS-MDI/DPI was switched to 1,320 μg of nebulized dexamethasone daily (1,600 μg as dexamathasone sodium phosphate). The doses of other medications were not increased and no new medications were added after the initiation of nebulizer therapy (the dose could be tapered or the medication could be stopped if sufficient symptomatic improvement was obtained). Patients taking systemic steroids, irrespective of the dosage or use of ICS-MDI/DPI, were also enrolled in the study to observe whether there was a steroid-sparing effect of nebulizer therapy (chronic steroid-dependent group). None of these patients had acute exacerbation and the dose of systemic steroids was always the minimum dose required to control symptoms. Any patient who was using oral steroids for other reasons was excluded from the study. If these patients were being treated with ICS-MDI/DPI therapy, it was switched to 1,320 μg of dexamethasone via nebulizer daily, while patients who were not receiving ICS-MDI/DPI therapy were also given nebulized dexamethasone. The oral steroid dose was tapered slowly if patients showed sufficient symptomatic improvement. Nebulized dexamethasone at the equivalent dose was administered to CVA/CPA patients with acute exacerbation due to triggering events (such as respiratory tract infection) who had persistent cough-predominant symptoms despite treatment with systemic corticosteroids (acute group). Treatment with systemic steroids was stopped or tapered if nebulizer therapy was effective. Immediate switching from oral prednisolone to dexamethasone via nebulizer without concurrent use of oral treatment was also attempted under careful observation. The nebulizer used in this study was an NE-U 22 (Omron, Tokyo). This is a mesh-type nebulizer producing an aerosol with a mean particle diameter of 4.3-4.5 μm,[13] which is similar to the particle size obtained with current jet nebulizers. Each patient received 0.2 mL of dexamethasone sodium phosphate (Decadron®, Banyu; 4 mg/mL dexamethasone sodium phosphate = 3.3 mg/mL dexamethasone) diluted in 1.8 mL of normal saline via nebulizer twice daily. The dose was administered in a continuous manner during inspiration and expiration, and patients were instructed to expectorate any intraoral fluid or saliva in order to reduce systemic absorption of the steroid.

This study was approved by the ethics committee of the International Medical Center of Japan and the National Hospital Organization Disaster Medical Center. Informed consent (verbal) was obtained from all participants in the study.

RESULTS

Eighteen patients with chronic cough (including 12 steroid-independent patients and 6 steroid-dependent patients) and 7 patients with acute exacerbation were analyzed in this study. All patients complained of an itchy sensation in the neck or upper anterior chest, which improved rapidly in the patients who responded to nebulizer therapy.

CHRONIC STEROID-INDEPENDENT GROUP (Table 1)

Of the 12 patients, 9 were receiving 800 μg/day of FP and 3 were on 800 μg/day of BUD. In 10 patients (83.3%), symptoms improved after treatment with dexamethasone via nebulizer, including 8 who showed a complete response and 2 with a partial re-

Table 1 Patient characteristics and outcomes in the chronic steroid-independent group

Case no.	Age (yr) and sex	Type of asthma	Dose of ICS Rx (μg)	Other medications		Side effects	Duration of ICS neb Rx (Mo)
				before neb	after neb		
Complete response							
1	36M	CVA	BUD 800	TH, B2	0	cough	2 terminated
2	61F	CPA	FP 800	TH, B2, AL	TH, B2, AL	GERD	3.5 terminated
3	46M	CVA	FP 800	TH, B2	0	GERD	2.5 terminated
4	26M	CVA	FP 800	TH, B2, AH	0	GERD	21 continued
5	39M	CVA	FP 800	TH, B2, AH	0	/	3 terminated
6	72M	CVA	FP 800	TH, B2	B2	/	1.5 terminated
7	33M	CVA	FP 800	TH, B2, AL	0	/	10 terminated
8	36M	CPA	FP 800	TH, B2	0	/	2 terminated
Partial response							
9‡	61F	CPA	FP 800	TH	TH	edema	35 continued
10	47M	CVA	FP 800	TH, B2, AL	TH, B2, AL	/	1 terminated
No response							
11	18M	CVA	BUD 800	TH	TH	/	0.5 terminated
12	57M	CVA	BUD 800	TH, B2	TH, B2	/	1 terminated†

ICS, inhaled corticosteroids; Rx, treatment; neb, nebulizer; CVA, cough-variant asthma; CPA, cough predominant asthma; BUD, budesonide; FP, fluticasone propionate; TH, theophylline; B2, beta-2 agonist; AL, anti-leukotriene; AH, antihistamine; GERD, gastroesophageal reflux disease.

† Switched to betamethasone nebulizer (1,600 μg per day) which was effective and has been continued for 18 months.

‡ In Case no.9, BUD suspension was used during ICS neb Rx.

sponse. Complete response was defined as the total disappearance of symptoms despite stopping nebulizer therapy or the almost complete resolution of symptoms with continuing nebulizer therapy. Partial response was defined as an obvious reduction of symptoms but some residual disturbance of daily activities. Seven patients showed a complete response and their nebulizer therapy was stopped (cases 1-3 and 5-8). In one patient with a partial response, cough showed rapid improvement after delivery of dexamethasone via the nebulizer. The patient then switched to inhalation of a BUD suspension (500 μg twice daily), which was imported by the patient from overseas for personal use, resulting in further improvement (case 9). This patient had edema of the face and extremities after receiving dexamethasone via the nebulizer, which improved after starting the inhaled BUD suspension. Treatment with BUD was continued for 3 months, and the daily dose of BUD was reduced to 250 μg twice daily during the latter half of this period without any reduction of efficacy. Subsequently, nebulized dexamethasone was reintroduced, resulting in slight worsening of the patient's cough and recurrence of edema.

In 2 patients in whom nebulized dexamethasone was effective (cases 4 and 7), treatment was switched from dexamethasone to betamethasone via nebulizer at a dose of 1,600 μg per day, resulting in further improvement of symptoms. In case 12, nebulized dexamethasone was not effective, but the same dose of nebulized betamethasone was effective and has been continued for 18 months.

CHRONIC STEROID-DEPENDENT GROUP (Table 2)

Of the 6 patients in this group, 2 were not using ICS, while 4 were on high doses of ICS-MDI/DPI. In 3 patients, nebulized dexamethasone was effective, including 2 complete responses and 1 partial response. A complete response was defined as a permanent reduction of oral steroid use, while a partial response was defined as a temporary reduction. In a patient with Churg-Strauss syndrome who had suffered from steroid-dependent asthma for 6 years (case 1), introduction of nebulized dexamethasone was followed by reduction of the dose of betamethasone from 0.75 mg to 0.25 mg daily and cessation of treatment with clenbuterol and montelukast. Respiratory symptoms resolved on the second day of nebulizer therapy and acute exacerbation (related to coughing fits) did not occur thereafter. Nebulized dexamethasone was ceased after 18 months due to good control of symptoms, but low-dose betamethasone was continued because of prior long-term administration. In case 2, symptoms improved rapidly and oral prednisolone was ceased within 2 weeks. Nebulizer therapy was also ceased after 2 months. Case 3 showed a partial response. Although a steroid-sparing effect was observed when the patient was taking 5 mg/day of prednisolone, symptomatic relief was temporary and fluctuating, so treatment was switched back to 800 μg of DPI-BUD daily after 12 months.

Table 2 Patient characteristics and outcomes in the chronic steroid-dependent group

Case no.	Age (yr) and sex	Type of asthma	Duration of steroid dependency (yr)	Dose of ICS Rx (μg)	Oral steroid dose (mg)		Side effects	Duration of ICS nebulizer Rx (Mo)
					before neb	after neb		
Complete response								
1	61M	CPA	6	BUD 800	BMS 0.75	BMS 0.25	/	18 terminated
2	75M	CPA	0.1	/	PSL 5	PSL 0	hoarseness	2 terminated
Partial response								
3	73F	CPA	1	BUD 800	PSL 12.5	PSL7.5	/	12 terminated
No response								
4	66M	CPA	11	FP 800	PSL 5	PSL 5	/	3 terminated
5	42M	CPA	7	/	BMS 0.5/1.0	BMS 0.5	/	8 terminated
6	72F	CPA	1.5	FP 800	PSL 7.5	PSL 7.5	/	1 terminated

ICS, inhaled corticosteroids; Rx, treatment; neb, nebulizer; CPA, cough predominant asthma; BUD, budesonide; FP, fluticasone propionate; BMS, betamethasone; PSL, prednisolone.

Table 3 Patient characteristics and outcomes in the acute group

Case no.	Age (yr) and sex	Type of asthma	Systemic steroid dose (mg)	Duration of steroid use (d)		Side effects	Duration of ICS neb Rx (Mo)
				before neb	after neb		
Complete response							
1	26F	CVA	PSL20	3	2	/	0.5 terminated
2	66M	CPA	PSL30	10	4	/	2 terminated
3	36F	CPA	PSL30	6	0†	/	1 terminated
4	42F	CPA	PSL30	5	0†	/	1 terminated
5	32F	CPA	PSL20	7	0†	/	3 terminated
Partial response							
6	68F	CVA	PSL20	11	0†	GERD, fatigue, appetite loss	1 terminated
7	61F	CVA	PSL20	7	0†	/	2.5 terminated

neb, nebulizer; ICS, inhaled corticosteroids; Rx, treatment; CVA, cough-variant asthma; CPA, cough predominant asthma; PSL, prednisolone; GERD, gastroesophageal reflux disease.

† In these patients, systemic steroids were stopped and switched to ICS via nebulizer, because of complete lack of improvement of cough by oral PSL.

ACUTE GROUP (Table 3)

All 7 patients showed improvement after introduction of nebulized dexamethasone, including 5 patients with a complete response and 2 with a partial response. A complete response was defined as the resolution of symptoms along with cessation of systemic steroid therapy. A partial response was defined as obvious improvement of symptoms without resolution. Despite receiving oral steroid therapy for 3-11 days before starting nebulized dexamethasone, all patients had intractable cough, causing sleep disturbance and exhaustion. In 5 patients (cases 3-7), administration of systemic steroids was stopped and treatment was switched to nebulizer therapy because of the complete lack of improvement of cough by oral prednisolone. Among the 5 complete responders, nebulizer therapy was stopped in 3 patients (cases 1-3) after complete resolution of symptoms. The other two patients (cases 4 and 5) were switched back to DPI therapy after obtaining good control of symptoms. Among the 2 partial responders, nebulizer therapy was stopped in case 6 due to side effects. In case 7, symptoms showed marked improvement, but nebulizer therapy was ceased after 2.5 months at the patient's request.

ADVERSE EVENTS

Nine adverse events occurred in 7 patients (28.0%), including 4 cases of heartburn, and 1 case each of hoarseness, edema, anorexia with upper abdominal pain, fatigability, and cough. Heartburn improved after stopping dexamethasone nebulizer therapy in 3 patients, while it was controlled with an H_2-blocker and nebulizer therapy was continued in 1 patient. Two of these patients had a history of gastroesophageal reflux disease. The patient with cough initially showed rapid improvement after starting nebulizer therapy, but then developed paradoxical nebulizer-induced mild cough. After nebulizer therapy was ceased, the patient had no further symptoms.

DISCUSSION

The present findings demonstrate that there may be a subpopulation of patients with CVA or CPA inadequately controlled by high dose ICS-MDI/DPI therapy who respond to nebulized ICS. Nebulized ICS has been employed to treat infants[14] and the elderly[15] who cannot properly use inhalation devices. Some studies have also shown the efficacy of this treatment for severe adult asthma. Previous studies have indicated that an oral steroid-sparing effect for typical asthma is seen in patients using 4,000 μg[16] or 4,000 to 8,000 μg of BUD inhaled suspension daily,[17] or else 1,000 to 4,000 μg on nebulized FP daily (with the strongest effect in the 4,000 μg group).[18] For acute exacerbation, 12,000[19] to 20,000 μg per day[20] of BUD inhaled suspension has been tried to control symptoms. The efficacy of particle deposition by nebulizers is not high, and single-dose studies using β2-agonists have suggested that a dose 4 to 8 times higher than the target dose is required in order to achieve equipotency between nebulizer therapy and MDI therapy with a spacer.[21-23] The lung deposition rate of BUD inhaled suspension is approximately 14%-16%[24] when a nebulizer is used with a breath synchronizer, which only allows generation of mist during inspiration to maximize the amount of drug inhaled by minimizing drug loss during expiration. Therefore, there would be less particle deposition throughout the airways when 1,000 μg of the drug was given via nebulizer without a breath synchronizer in one of our chronic steroid-independent patients (case 9) compared with a deposition rate of 32% during treatment with 800 μg of BUD via turbuhaler.[25] Thus, the symptoms of our patient were more effectively suppressed by deposition of fewer BUD particles via nebulizer than by deposition of more particles with DPI. Also, at least in case 9, it was suggested that 1,320 μg of nebulized dexamethasone daily is less potent than 1,000 μg of BUD inhaled suspension, and this result is supported by the report that the topical anti-inflammatory potency of dexamethasone is about 1/9 of that of BUD based on their relative binding affinities for the rat glucocorticoid receptor.[26]

The better clinical outcome obtained with nebulized ICS, despite deposition of fewer particles throughout the airways than with DPI, suggests that a change in the distribution of corticosteroid particles in the central airway was achieved by nebulizer therapy. The single inhalation experiment in the tracheobronchial model revealed that the distribution of particles is not uniform in the central airway.[3-7] Bifurcations in the proximal tracheobronchial tree are the main sites of deposition because the particles have considerable inertia so that their trajectory deviates from fluid streamlines.[3,5] The region immediately distal to the larynx is another site of enhanced particle deposition because of the laryngeal jet.[3] A study of aerosol behavior using laser Doppler velocimetry and a fluorescent dye revealed marked deposition within the first 3-4 cm of the trachea.[6] Another study of intrabronchial and intratracheal deposition using a hollow cast of a human larynx plus tracheobronchial tree showed that there is a deposition 'hot-spot' in the trachea located 2 cm below the larynx and that deposition is also enhanced at the tracheal bifurcation due to changes of air flow at this region.[4] Most of the deposition of particles in the trachea occurs within 2 cm distal to the larynx, accounting for 60% of total intratracheal deposition. This pattern of deposition was reported to be independent of flow rate (at 15-60 l/min) and particle size (>2 μm),[4] while total intratracheal deposition increases with the flow rate.[6] Then deposition decreases in the next part of the trachea and is uniform for about 6 cm, after which deposition increases gradually as the trachea attains its transitional elliptical shape prior to dividing into the main bronchi. In both the trachea and the main bronchi, the distribution of air flow and turbulence is not uniform,[7] and enhanced accumulation of particles on the inner sides of the main bronchi is common.[27] On the other hand, the main sites of particle deposition on expiration are the lumens of the parent branches above the bifurcations.[28,29] This means that the lower part of the trachea, where there is little deposition of particles during inspiration, is covered during expiration provided that there are enough particles remaining in the airway at the time of the expiratory phase. Current devices for delivery of ICS, such as the MDI or the DPI, require the total dose to be inhaled at once. As a result, the distribution of the inhaled particles might be far from uniform (as shown by previous single-inhalation experiments), with few particles in the central airways at the end-inspiratory phase and limited deposition on the mucosa of the trachea in the expiratory phase. To date, the distribution of particles deposited by nebulizer therapy has never been reported (personal communication). With nebulizer therapy, the central airways are filled with particles even during the end-inspiratory phase and the chance of deposition on the mucosa during the expiratory phase may be increased, suggesting that nebulizer therapy may achieve a more uniform distribution of the particles within the trachea.

Airway sensory receptors, such as rapidly adapting airway mechanoreceptors (RARs) and C-fiber endings, are not only distributed in the bronchi but are also found in the trachea and the larynx,[8] and enhanced afferent excitability of these receptors is associated with inflammation.[9] Tracheitis is commonly associated with diseases that cause cough, and an itchy sensation in the neck and upper anterior chest indicates inflammation of the trachea.[10] In our experience, rapid disappearance of such an itchy sensation in the upper anterior chest and neck after nebulizer ICS therapy was observed in patients who responded

to this therapy. These findings suggest that the trachea might have been treated more effectively by nebulizer therapy due to a change in the distribution of drug particles. It is possible that the patients with CVA or CPA who failed to respond or responded partially to ICS-MDI/DPI in this study might have had residual tracheal inflammation whereas their bronchial inflammation was controlled. This suggests that the efficacy of ICS therapy should not only be assessed from lung deposition of drug particles but also from tracheal deposition in patients with intractable asthmatic cough.

The increased benefit of nebulized dexamethasone could also be a result of greater systemic absorption[30] than after treatment with DPI-FP or DPI-BUD. However, this could not completely explain the improvement noted because our study showed that nebulized dexamethasone was more beneficial for acute exacerbation of CVA and CPA than administration of oral corticosteroids. Also, the reduction of the oral steroid dose in the steroid-dependent group was greater than the amount absorbed (a decrease of 0.5 mg/day of betamethasone in case 1 or 5 mg/day of prednisolone in cases 2 and 3). The other possibility is that a more homogenous distribution of drug particles in the peripheral airways can be achieved by nebulizer therapy, which leads to better control of cough. The mechanism of cough in CVA has been suggested to involve bronchospasm,[31] similar to that in typical asthma, because infiltration of eosinophils,[32] thickening of the subepithelial layer in subsegmental bronchi,[33] and an increase of eosinophils in BAL fluid[32] have also been reported in CVA and these patients respond to bronchodilator therapy. On the other hand, O'Connel *et al*. hypothesized that CVA patients had inflammation limited to the large airways,[34] which is where cough receptors are most abundant.[8] Rapid disappearance of an itchy sensation in the upper anterior chest and throat of our patients suggests that the mechanism of cough involves more than just the peripheral airways.

In general, systemic corticosteroid therapy is effective for acute exacerbation of CVA as well as for typical asthma, but a few patients are refractory to such therapy, as seen in our acute group. We found rapid improvement only after using nebulized dexamethasone to treat such refractory patients with acute exacerbation of CVA or CPA, regardless of whether it was combined with oral steroids or they were switched to nebulizer therapy alone. This suggests that the improvement of symptoms was not only related to systemic effects of corticosteroid therapy. The exact mechanism involved is unknown, but it is possible that steroid levels in the trachea were low with systemic therapy in our patients, making nebulized ICS a possible alternative medication for tracheitis-related exacerbation of CPA/CVA.

During follow-up, the effect of nebulized ICS did not always persist. Administration of a dose of 1,320 μg of dexamethasone via nebulizer is sufficient to treat the trachea, but this treatment is less potent than 800 μg of inhaled FP or 800 μg of inhaled BUD, so the anti-inflammatory effect on the entire airway tree may be weaker. Therefore, treatment with nebulized dexamethasone should be accompanied with or switched to ICS-MDI/DPI, depending on the clinical course of the patient. Furthermore, gastroesophageal reflux is a side effect of nebulized dexamethasone that might contribute to the recurrence of cough. Another possibility is that additives such as sulfites in the dexamethasone solution could act as irritants during long-term treatment.[15] The higher rate of adverse effects with dexamethasone nebulizer therapy compared to ICS-MDI/DPI therapy suggests that the safety of this method for long-term management of CVA or CPA is uncertain. On the other hand, long-term inhalation of BUD suspension has been clinically proven to be safe.[35,36] This drug was not available in Japan when the present study was conducted, so its clinical benefit for the treatment of intractable CVA and CPA should be further evaluated in future studies.

In summary, nebulized ICS was more effective than DPI in certain patients with CVA or CPA. A change in the distribution of drug particles delivered via a nebulizer with increased deposition in the trachea is thought to be the main mechanism leading to improvement. Patients with CVA or CPA who fail to respond or only respond partially to ICS-MDI/DPI therapy might have residual inflammation in the trachea although their bronchial inflammation is controlled. Tracheitis should be considered separately from bronchitis to achieve better awareness of the existence of a subgroup of CVA and CPA patients who can benefit from nebulized ICS.

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