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ORIGINAL ARTICLE

Aerosol Characteristics of Admixture of Budesonide Inhalation Suspension with a Beta2-Agonist, Procaterol

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ABSTRACT

Background: Nebulized drugs for asthma treatment are often mixed together in order to simplify inhalation regimens, although not recommended. We therefore evaluated aerosol characteristics and physicochemical stability of the admixture of an inhaled corticosteroid suspension with a beta2-agonist solution.

Methods: An 8-stage cascade impactor was used to measure the particle size distribution of admixture of Pulmicort® Respules® (budesonide, 0.5 mg/2 mL) with Meptin® Inhalation Solution Unit (procaterol hydrochloride, 30 μg/0.3 mL) from a jet nebulizer, PARI LC Plus®. Concentration of each drug was assayed with high-pressure liquid chromatography. Physicochemical compatibility was also assessed up to 24 hours after mixing.

Results: With regard to budesonide, impactor parameters such as mass median aerodynamic diameter (MMAD) and respirable mass (RM) were comparable between admixtures and single-drug preparations (2.92 ± 0.03 vs 2.99 ± 0.14 μm, 146.8 ± 2.9 vs 147.6 ± 8.2 μg, respectively). On the other hand, delivery rates of procaterol increased when admixed with budesonide suspension, resulting in significantly higher RM (15.1 ± 0.8 vs 10.2 ± 0.5 μg, $p < 0.01$). Variations from initial concentration in the percentages of drug remaining at any time point were less than 10%, and there were no appreciable changes in pH of the admixtures for up to 24 hours.

Conclusions: There is a possibility that admixture might influence of aerodynamic characteristics of procaterol, but not budesonide. *In vivo* data will be needed for the clinical implications of our findings.

KEY WORDS

asthma, beta2-agonist, drug admixture, inhaled corticosteroid, nebulizer

INTRODUCTION

Nebulizers are widely used for the inhalation of drugs in a variety of respiratory diseases such as asthma. The efficacy of inhalation therapy using a nebulizer is influenced by a number of factors, including the design of the device and the characteristics of the drug solution.[1] When patients need several kinds of nebulized drugs, a substantial proportion of them might admix medications, because nebulization is a time-consuming task, even if the effect of co-administration on aerosol output and bioactivity are poorly studied. Indeed, one survey of patients with cystic fibrosis showed that a quarter of them reported mixing of medications.[2]

Inhaled corticosteroids (ICS) are the first line therapy for children with persistent asthma, because asthma is characterized by chronic inflammation of the airways.[3] Budesonide inhalation suspension (BIS) is one of the ICSs available for nebulization, and clinical studies demonstrated its efficacy and safety in the long-term management of young children with asthma.[4-6] Furthermore, BIS has been reported to be useful for the treatment of acute episodes of asthma.[7] In addition to ICS, a beta2-agonist is another important medicine, which has been used not only as a reliever but also as a controller. A recent study showed the efficacy of a regimen using a budesonide/for-

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moterol dry-powder inhaler for both maintenance and as-needed symptom relief in older children with asthma.[8] For younger children, nebulization is preferable to a meter-dosed or dry-powder inhaler. Furusho showed that regular inhalation of the combination of nebulized sodium cromoglycate and a beta2-agonist, salbutamol was superior to either cromoglycate alone or salbutamol alone for the treatment of moderate-to-severe asthma in children.[9] Thus, a beta2-agonist might be added to BIS as a single nebulization formula, and a couple of clinical studies had been done using an admixture of BIS and a beta2-agonist.[10,11] However, systemic evaluations regarding the effect of co-administration of these drugs on physicochemical stability are limited,[12] and there has been no study which looked into the effect of the admixture on aerosol characteristics of each drug. Therefore, we conducted an *in vitro* study, using a combination of BIS and a beta2-agonist, procaterol. Procaterol is a selective and full beta2-agonist, which has been shown to elicit anti-inflammatory effects on eosinophils in combination with inhaled corticosteroids in vitro.[13,14]

METHODS

DRUGS AND NEBULIZER

BIS, Pulmicort® Respules® 0.5 mg/2 mL (AstraZeneca, KK, Osaka, Japan) and a beta2-agonist, procaterol inhalation solution, Meptin® Inhalation Solution Unit 30 μg/0.3 mL (Otsuka Pharmaceutical, Tokyo, Japan) were used in this study. The following formulas were prepared: 2 mL BIS combined with 0.3 mL saline (0.9% NaCl), 2 mL saline combined with 0.3 mL procaterol solution, and 2 mL BIS combined with 0.3 mL procaterol solution. These preparations were nebulized via a PARI LC Plus® nebulizer (PARI GmbH, Starnberg, Germany) driven by a PARI TurboBoy N® compressor (PARI GmbH).

MEASURING AEROSOL CHARACTERISTICS

To measure delivery rates, a nebulizer was held in upright position by a ring stand and was connected with a tube to a glass bottle. Aerosol droplets of the prepared medications were collected during continuous nebulization, and the concentration of each drug was assayed with high-pressure liquid chromatography (HPLC LC-2010CHT, Shimadzu, Kyoto, Japan). Delivery rates were calculated as percentages of nominal dose.

Particle size distribution of each drug was analyzed with an 8-stage cascade impactor (Anderson Cascade Impactor, Coply Scientific, Nottingham, UK). Aerosol droplets were collected in the impactor at a flow rate of 28.3 L/min with the corresponding cut-off points; 0.4, 0.7, 1.1, 2.1, 3.3, 4.7, 5.8, and 9.0 μm. Each stage of the impactor was washed with a solvent and the concentration of each drug in the solvent was assayed with HPLC. Mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD), respirable fraction (RF; percent of particles in the 0.4-5 μm range), and respirable mass (RM; total drug output x RF) were calculated, according to the European Pharmacopoeial method.

STABILITY ASSESSMENTS

Prepared admixtures were stored in a 10-ml glass test tube at room temperature under scattered light. Stability of each preparation was assessed 1, 2, 4, 8, and 24 hours after admixture. Concentrations of drugs were assayed as mentioned above, and pH values of the admixtures were obtained with a pH meter (F-22, HORIBA, Ltd., Kyoto, Japan).

STATISTICAL ANALYSIS

Each test was performed three times. Comparisons of aerosol characteristics between the prepared medications were tested using an independent-sample *t*-test. Statistical significance was assumed to be $p < 0.05$.

RESULTS

AEROSOL CHARACTERISTICS

The addition of procaterol solution to BIS did not affect the delivery rate of budesonide (Fig. 1). Impaction analysis also revealed no differences in aerosol particle size distribution of budesonide between the admixtures and single-drug preparations (Fig. 2a). Calculated impactor parameters regarding budesonide were also comparable between the admixtures and single-drug preparations (Table 1). On the other hand, significantly higher amount of procaterol was delivered when admixed with BIS compared with single-drug preparations ($p < 0.01$, Fig. 1). Impaction analysis showed that distribution rates of procaterol were increased in smaller particle size (Fig. 2b), resulted in significantly higher RM in the admixtures ($p < 0.01$, Table 2).

STABILITY

Variations from initial concentration in the percentages of drug remaining at any time point were less than 10%, and there were no appreciable changes in pH of the admixtures during 24 hours (Table 3).

DISCUSSION

Although BIS has been used clinically in admixtures with beta2-agonists,[10,11] systemic evaluations regarding the effect of admixtures on the aerosol characteristics and physicochemical stability are limited. Because of the differences in physical characteristics between suspension (BIS) and solution (procaterol),[1] there is a possibility that admixing these drugs could have some effect on the aerosol characteristics and physicochemical compatibility of them. With regard to budesonide, we did not find any evidence that addition of procaterol solution to BIS altered delivery rate and aerosol particle size distribution of budesonide. Reid *et al.* showed that treatment with the combina-

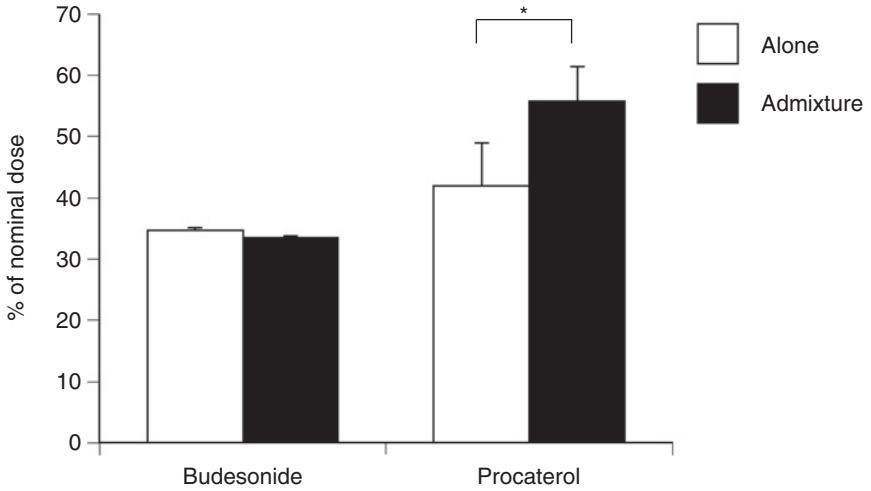

Fig. 1 Delivery rates of budesonide and procaterol from admixtures or single-drug preparations. Results are shown as mean + SD (n = 3). *p < 0.01 by t-test (comparison of procaterol alone against admixture).

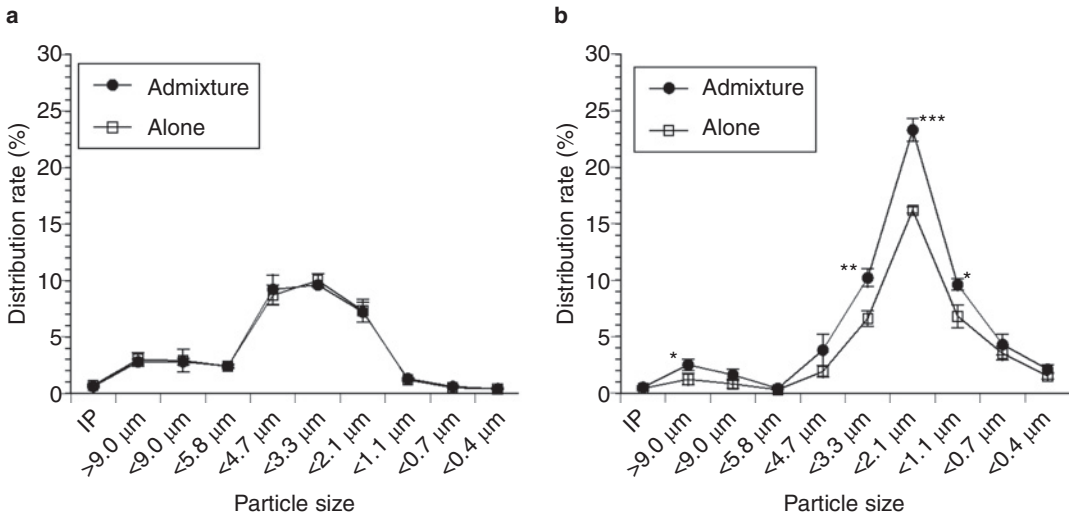

Fig. 2 Effect of admixture on particle size distributions of budesonide (**a**) and procaterol (**b**). Results are shown as mean ± SD (n = 3). *p < 0.05, **p < 0.01, and ***p < 0.001 by t-test (comparison of admixtures against single-drug preparations). Abbreviation: IP, induction port.

tion of BIS plus beta2-agonists (terbutaline or salbutamol) for longer than 6 months did not have a significant impact on linear growth in asthmatic children younger than 3 years old.[10] Although they did not have a treatment arm consisting of children who were treated with BIS alone, our results suggest that the admixture itself could not adversely affect linear growth. Furthermore, the admixture had no effect on the stability of budesonide, consistent with the previous study that found chemical compatibility of budesonide inhalation solution for up to 30 min with commonly used nebulized medications such as albuterol, cromolyn, and ipratropium.[12]

In contrast to budesonide, delivery rate of procaterol significantly increased in a combination with BIS, resulting in higher RM of procaterol. There is one possibility that Polysolvate 80, a nonionic surfactant contained in BIS, might cause this change. These results lead to concern about whether higher dose of beta2-agonist might cause adverse effects. We previously evaluated whether differences in nebulizer performance could influence safety and efficacy of inhaled beta2-agonist in children with asthma, using two different types of nebulizers with a two-fold difference in their delivery rates.[15] Contrary to our assumption, no adverse effects were found in all the

Table 1 Aerosol characteristics of budesonide

Preparation	MMAD (μm)	GSD	RF (%)	RM (μg)
BIS + Saline	2.99 ± 0.14	2.12 ± 0.02	74.9 ± 2.1	142.7 ± 9.1
BIS + Procaterol	2.92 ± 0.03	2.14 ± 0.00	75.5 ± 0.4	141.9 ± 3.8

Results are shown as mean ± SD (n = 3).

Abbreviations: BIS, budesonide inhalation suspension; MMAD, mass median aerodynamic diameter; GSD, geometric standard deviation; RF, respirable fraction; RM, respirable mass.

Table 2 Aerosol characteristics of procaterol

Preparation	MMAD (μm)	GSD	RF (%)	RM (μg)
Procaterol + saline	1.56 ± 0.15	2.15 ± 0.07	89.6 ± 2.1	10.2 ± 0.5
Procaterol + BIS	1.69 ± 0.04	2.23 ± 0.09	87.6 ± 2.0	15.1 ± 0.8*

*p < 0.01 by t-test (comparison of procaterol alone against admixture).

Results are shown as mean ± SD (n = 3).

Abbreviations: BIS, budesonide inhalation suspension; MMAD, mass median aerodynamic diameter; GSD, geometric standard deviation; RF, respirable fraction; RM, respirable mass.

Table 3 Physicochemical compatibility of the admixture of budesonide inhalation suspension and procaterol

a) Recovery rates (%)

	1	2	4	8	24 (hr)
Budesonide	96.2 ± 2.4	93.0 ± 6.6	96.4 ± 0.4	96.5 ± 0.3	96.8 ± 1.1
Procaterol	101.1 ± 3.8	101.5 ± 2.8	102.0 ± 6.5	98.5 ± 1.4	101.5 ± 0.8

b) Changes in pH

	pre	1	2	4	8	24 (hr)
Budesonide	4.5 ± 0.0	4.0 ± 0.0	4.0 ± 0.0	4.1 ± 0.0	4.1 ± 0.0	4.1 ± 0.0
Procaterol	3.5 ± 0.0					

Results are shown as mean ± SD (n = 3).

subjects, and efficacy was comparable between the subjects who inhaled with either nebulizers. To date, no controlled study has been undertaken to determine the optimal dose of inhaled beta2-agnoist for the treatment of children with asthma. Therefore, it is difficult to say that high RM of procaterol in this study would increase the frequency or extent of the adverse effects.

In this study, we showed a possibility that admixture of BIS and procaterol solution might affect aerodynamic characteristics of procaterol, but not budesonide. To address the question whether these *in vitro* findings are clinically relevant or not, further clinical studies are needed in terms of efficacy and safety of the combination treatment with nebulized ICS and beta2-agonist.

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