—Regular Articles—

Clinical Characteristics of Asthmatic Patients Prescribed Various β-Agonist Metered-Dose Inhalers at Yamagata University Hospital

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To determine the prescription characteristics of β-agonist metered-dose inhalers (MDI), we retrospectively investigated all prescriptions containing one of five types of β-agonist MDIs available at Yamagata University Hospital in 1997, as well as patients' characteristics. The total number of asthmatic patients was 225 (age, 11—79, mean, 47.2) in 1997. Fenoterol MDI was prescribed to patients who visited the hospital at regular periods and had more severe asthma. Isoprenaline MDI also was not prescribed for first-time patients. Patients who were prescribed tulobuterol MDI had mild or moderate asthma and some of them were only occasional or first-time visitors. Salbutamol and procaterol MDIs were also prescribed for first-time patients; however, tulobuterol MDI was the most frequently prescribed for first-time patients. Patients prescribed fenoterol and isoprenaline MDIs had adequate knowledge of proper asthma management, because sufficient information had been provided about the use of MDIs in the past. Patients prescribed tulobuterol MDI should be provided with detailed instructions because they had little knowledge of handling MDIs and self-management of asthma as many of them were first or intermittent visitors. Patients prescribed salbutamol or procaterol MDIs should be evaluated regarding their past medications and some of them should be instructed regarding the use of the MDI. Although these clinical aspects might be applicable only to our hospital, the same or other prescription patterns will be found in other hospitals and/or by other physicians. Adequate instructions to individual patients who are prescribed a particular β-agonist MDI should be provided by the medical staff, especially to outpatients, to reduce hospitalization and death from asthma.

Key words——β-agonist metered-dose inhaler; clinical characteristics; pharmaceutical instruction; asthmatic patients

INTRODUCTION

Anti-inflammatory drugs have become a fundamental component of treatment for bronchial asthma; however, a β-agonist metered-dose inhaler (MDI) is indispensable for relief from an asthma attack.[1,2] Unfortunately, β-agonist MDIs have serious clinical problems. One such problem is incorrect inhalation manoeuvres indicating the need for comprehensive patient education.[3,4] Another problem relates to a potentially higher risk of death from asthma posed by some β-agonists due to the patient's dependency on and excess use of these inhalers, which was initially noted with the regular and excessive use of isoprenaline[5] and later with fenoterol.[6—8] In this regard, whether fenoterol MDI increases the risk of death from asthma is still controversial.[9—11] Accurate conclusions have not been made; however, proper instructions on the inhalation manoeuvres using β-agonist MDIs as well as other useful information on self-management by asthmatics are undoubtedly necessary for reducing deaths from asthma and preventing exacerbation of the disease.[12] Knowledge of the clinical characteristics of patients who were prescribed a particular β-agonist MDI would be useful to the medical staff in presenting pharmaceutical instructions. In the present study, all prescriptions in 1997 that included β-agonist MDIs were examined, and the combined asthma medications and the severity of asthma were investigated.

METHODS

1. Information about β-Agonist MDIs Used in Yamagata University Hospital and Assumed Frequencies of Use

The β-agonist MDIs used in Yamagata University Hospital and their profiles are listed in Table 1. All prescriptions in 1997 were examined and those containing β-agonist MDIs were selected for analysis. The numbers of patients in each β-agonist MDI group were comparable, but the prescribed canister numbers were not comparable because the number of actuations specified by the manufacturer per canister was different for each β-agonist MDI as shown in Table 1. Therefore, an assumed frequency of use (mean puff times per day per patient) of each β-agonist MDI was calculated using the following formula and used for comparison among the five β-agonist MDIs.

Table 1. β-Agonisa MDIs Available at Yamagata University Hospital

β-Agonist	Abbreviations	Preparations	Actuation dose per puff (μg)	Specified actuation number	Adoption perios (y)
Fenoterol hydrobromide	Feno	Berotec® Metered Areosol	200	100	>10
Isoprenaline sulfate	Isop	Stomerin® D*	100	60	>10
Procaterol hydrochloride	Proc	Meptin® Air	100	100	9
Salbutamol sulfate	Salb	Saltanol® Inhaler	100	79	7
Tulobuterol	Tulo	Hokunarin® Aerosol	100	100	2

* Combined with dexamthasone (33 μg/puff) and atropine methylbromide (6.7 μg/puff).

Assumed frequency of use (mean number of puffs /day/patient)

$$= \frac{\text{number of canisters used per patient} \times \text{specified number of puffs}}{365}$$

2. Analysis Severity of Asthma

All patients prescribed β-agonist MDIs in 1997 were selected and the severity of asthma in these patients was determined depending on the classification for the severity of asthma in ''Asthma management and prevention'' (1995). Asthma severity was scored as mild: 1, moderate: 2, and severe: 3, for statistical comparison of patients. Intermittent severity patients were included in mild severity. We also recorded the combined use of other asthma medications in these patients, in addition to β-agonist MDIs. Oral corticosteroids, oral β-agonists, sustained release theophylline preparations, inhalation corticosteroid (beclomethasone dipropionate) and antiallergic drugs were selected as other asthma medications, and the combination ratios were compared with each β-agonist MDI. Finally, we also determined the frequency of changes of the β-agonist MDI in the same patient in 1997.

3. Statistical Analysis

Data were expressed as mean (SD). One-way factorial analysis of variation was employed as the statistical analysis for comparison of data for each β-agonist MDI. Scheffe's F test was used as a post-hoc test with StatView ver. 4.51 for Macintosh. A p value <0.05 was considered statistically significant.

RESULTS

1. Patients Characteristics

Table 2 summarizes the characteristics of patients who were prescribed β-agonists. The total number of canisters dispensed in 1997 was 1,827.

2. Prescription Profiles of Each β-agonist MDI

The number of prescribed patients and canisters and the mean number of prescribed patients per month in 1997 for each β-agonist MDI are presented in Table 3. The number of patients prescribed procaterol MDI was the highest; however, fenoterol MDI canisters were the most frequently prescribed among the five β-agonist MDIs in 1997. The mean numbers of patients per month using fenoterol, procaterol and salbutamol MDIs were almost equal. Isoprenaline and tulobuterol MDI were the least prescribed, as evident by the small number of canisters of both. The proportions of patients on treatment per month to the total number of patients

Table 2. Characteristics of Patients Prescribed β-Agonist MDIs in 1997

n	225
Males-females	140/85
Age (years)	47.2(19.8)*
Diseased preiod (years)	9.6(7.0)*
Severity	
Mild	132
Moderate	67
Severe	26
Type	
Atopic	121
Non atopic	104

* Data are mean (SD).

Table 3. Number of Prescribed β-Agonist MDIs, Number of Patients and Mean Number of Patients per Month

β-Agonist MDI	Number of canisters	Nimber of patients	Mean nimber of patients per month*
Feno	503	48	19.0(4.4)
Isop	221	18	7.5(2.0)
Proc	474	70	18.6(2.6)
Salb	424	48	18.8(2.5)
Tulo	205	50	11.3(1.7)

* Data are mean (SD).

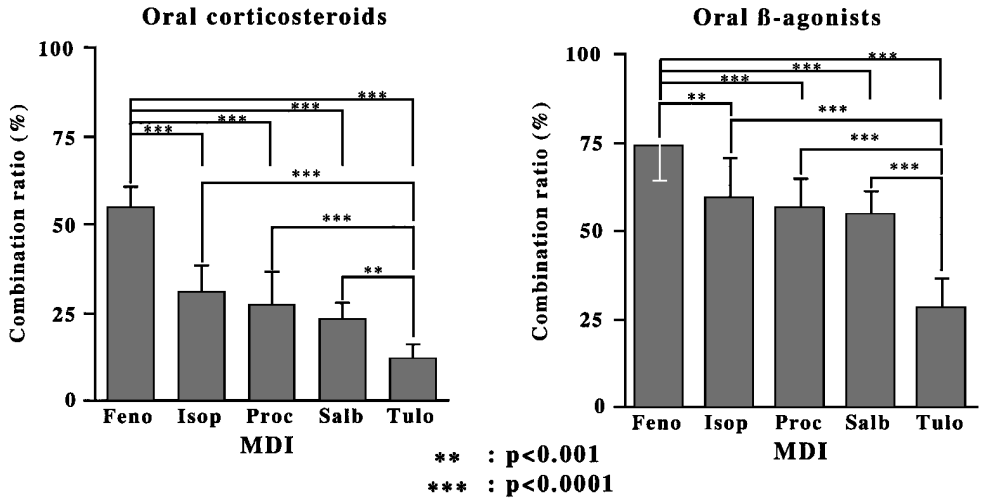

Fig. 1. Mean Combination Ratio of Oral Corticosteroids (Left) and Oral β-Agonists Ratio (Right) per Month in 1997
Data are mean (SD).

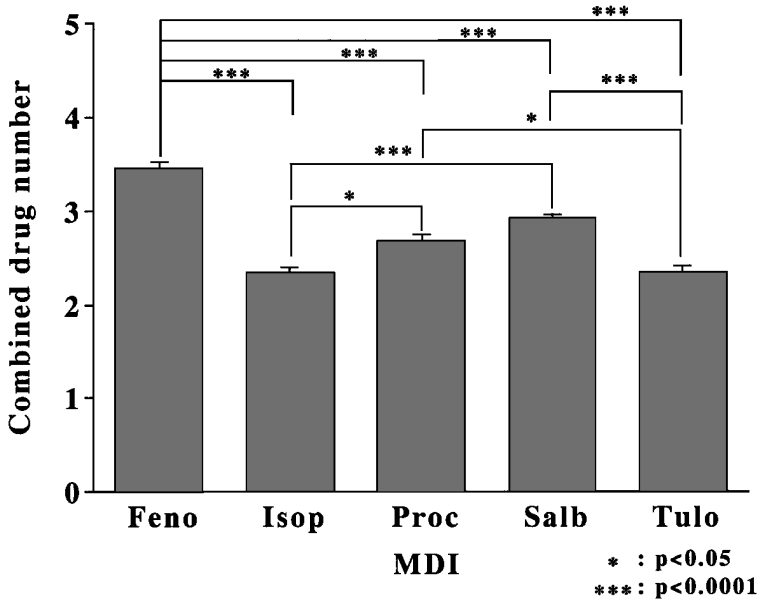

Fig. 2. Number of Asthma Medications Combined with β-Agonist MDIs in 1997
Oral corticosteroids, oral β-agonists, inhalation steroid, sustained release theophylline preparations and anti-allergic agents were selected as asthma medications. Data are mean (SD).

prescribed tulobuterol and procaterol MDIs were less than those of the other three β-agonist MDIs. Consequently, patients using tulobuterol and procaterol MDIs did not need a β-agonist MDI at every visit.

3. Combination of Asthma Medications with β-Agonist MDIs

The combination ratio of oral corticosteroids in patients prescribed fenoterol MDI was significantly the highest while that with tulobuterol MDI was the lowest, compared to other β-agonist MDIs (Fig. 1). The same results were also noted in oral β-agonists; however, the combination ratio of each β-agonist was higher than the corresponding ratio with oral corticosteroids. Concerning the kinds of asthma medications prescribed in combination with β-agonist MDI, fenoterol MDI was significantly the most frequently prescribed drug, while tulobuterol MDI was significantly the least used, compared to other β-agonist MDIs (Fig. 2).

4. Severity of Asthma and Assumed Frequency of Use of β-Agonist MDI

The severity scores of patients with asthma are shown in Table 4. The severity score of patients using fenoterol MDI was significantly higher than that of

Table 4. Severity Score of Asthma, Assumed Frequency of Use and Number of First Prescribed Patients fro Rach β-Agonist MDI

β-Agonist iDI	Severity score*	Assumed frequency of use per day**	First prescribed for patients
Feno	1.98(0.77)	2.87(3.39)	0
Isop	1.41(0.71)	2.02(2.08)	0
Proc	1.54(0.77)	1.86(2.53)	9
Salb	1.50(0.56)	1.93(2.36)	9
Tulo	1.21(0.41)†	1.12(1.73)††	15

* : Severity was scored as mild: 1, moderate: 2, severe: 3 and expressed as mean (SD).
** : Assumed drequency of use was calculated as described in the methods and expressed as mean (SD) per day.
† $p<0.05$ compared to Feno, †† $p<0.01$ compared to Feno.

Table 5. Changes in Prescribed β-Agonist MDI in 1997

Patient No.	M/F	Age	Severity	Change
1	F	51	Moderate	Proc→Feno
2	M	55	Severe	Isop→Proc
3	M	21	Moderate	Proc→Feno
4	M	41	Moderate	Feno→Proc
5	M	26	Moderate	Feno→Proc
6	F	21	Moderate	Feno→Proc
7	F	46	Moderate	Feno→Salb
8	F	62	Moderate	Feno→Tulo
9	F	74	Mild	Proc→Feno

patients with procaterol and tulobuterol MDIs. The severity score in patients prescribed fenoterol MDI tended to be higher than those prescribed isoprenaline and salbutamol MDIs ($p=0.075$ and 0.054, respectively). Furthermore, the assumed frequency of use of fenoterol MDI was higher and that of tulobuterol MDI was lower than that of other β-agonist MDIs (Table 3). Fenoterol and isoprenaline MDIs were not prescribed to first-visit patients (Table 3).

5. Death from Asthma and Change in β-Agonist MDI in Prescriptions

No asthma deaths were encountered at least in the 5-year period preceding the investigation. Changes in the prescribed β-agonist MDI preparation were noted in nine patients in 1997 (Table 5). Among these, three patients changed to fenoterol MDI from another MDI, and five changed to other β-agonist MDIs from fenoterol MDI. The last patient changed from isoprenaline MDI to procaterol MDI. The three patients who changed to fenoterol MDI were initially prescribed fenoterol MDI at first consultation and changed to another β-agonist MDI before 1997.

DISCUSSION

There is no doubt that β-agonist MDIs are essential for the treatment of asthmatic patients and for improvement of asthma attacks by self-inhalation. However, it has been reported that the use of isoprenaline MDI was associated with increased frequency of asthma deaths because of its non-selectivity for β_1 and β_2 receptors and regular, excessive use.[5] Similar results have also been reported recently for fenoterol MDI.[6—8] However, with regard to fenoterol MDI, previous studies showed that this medication did not cause an increase in death from asthma classified according to the severity of patients who were prescribed other β-agonist MDIs.[10] Furthermore, such a relationship has been observed only in Australia.[11] The arguments regarding the relationship between fenoterol MDI and increased risk of death from asthma are still inconclusive; however, our analysis showed that fenoterol MDI is actually the most frequently prescribed asthma medication in our hospital. In addition, death from asthma has certainly been observed in patients using β-agonist MDIs other than fenoterol MDI.[10] Consequently, patient education with regard to the use of β-agonist MDIs and self-treatment of asthma attacks is essential for reducing deaths from asthma with any type of β-agonist MDIs. On the other hand, understanding the characteristics of patients who are prescribed the respective β-agonist MDI is helpful in order to provide the best instructions on how to use these medications. Therefore, we investigated all prescriptions containing β-agonist MDIs in Yamagata University Hospital in 1997 and the characteristics of these patients.

Our results showed that fenoterol MDI was the most frequently prescribed β-agonist MDI, although there were no patients who were prescribed this medication for the first consultation among our group for 1997. Asthma in patients using fenoterol MDI tended to be more severe than in patients using other MDIs, because they had high asthma severity scores and assumed frequency of use. The same patients also tended to show a high combination ratio of oral corticosteroids or other asthma medications with β-agonist MDI within the prescription. Among the β-agonist MDIs, isoprenaline MDI was the least prescribed, and patients using this medication visited Yamagata University Hospital frequently throughout the year. Consequently, patients who were prescribed fenoterol and isoprenaline MDI are expected to have good knowledge of the self-treatment of asthma attacks and other asthma-related self-management.

This conclusion stems from the fact that they had already been provided with instructions on the fundamental manoeuvres required for use of β-agonist MDIs by pulmonary physicians and other members of the medical staff including pharmacists.

Tulobuterol MDI tended to be prescribed on the first visit and for mild asthmatics, and some of these patients did not find it necessary to visit the hospital on a regular basis for medications. The total number of patients using tulobuterol MDI in 1997 was similar to that for fenoterol and salbutamol MDI; although fewer patients per month visited the hospital compared to those using the other two MDIs. Hence, patients who were first prescribed tulobuterol MDI should be given extensive instructions regarding the inhalation manoeuvres used for the MDI because of the limited time visiting the hospital. Asthma severity in patients prescribed procaterol or salbutamol MDIs varied widely, and these patients visited the hospital at regular intervals or were prescribed the medication during their first visit to our hospital. Therefore, these patients should also be provided with thorough instructions regarding the use of these medications and day-to-day management of asthma.

Patients need to have spare β-agonist MDIs canisters available in living rooms, bedrooms, cars and offices or anywhere asthma attacks might occur. Previous studies have shown that many patients use MDIs more frequently than specified by the manufacturer.[13] The assumed frequency of use of a β-agonist MDI per day estimated in our study was not equal to the actual frequency of use. However, the order of actual frequency of use for each β-agonist MDI did not differ from the order determined in our study. A higher assumed frequency of use of the β-agonist MDI suggests that the frequency of asthma worsening in patients who were prescribed a particular β-agonist MDI was high.

Our results also showed that asthmatics preferred to remain on the same MDI rather than change their β-agonist MDI prescribed first. Patients did not change their β-agonist MDIs prescribed on the first visit, because they were satisfied with their effects and developed experience(s) in which they had been rescued from near-death from asthma and/or severe asthma attack. Several factors, such as management errors,[14,15] health service accessibility[16] and reduced chemosensitivity,[17] contribute to deaths or near-death from asthma. Sly suggested that optimal management of asthma should reduce any rise in the asthma death rate.[18] Although there were no asthmatic deaths during the five years preceding the present investigation, a number of asthmatics visited the emergency room in our hospital because of exacerbation of asthma attacks. Considerable patient education is essential on the use of MDIs, including not only β-agonists but also glucocorticoids, in treating asthma as an inflammatory disease of the airways and on the importance of regular use of medication even in the absence of any subjective symptoms. Pharmacists could be helpful in patient education as a member of the medical staff, similar to nurses.[19—21] While pulmonary physicians provide some advice to the patients at every consultation, it is often difficult to give adequate information and to inquire about the patient's knowledge of inhalation manoeuvres during the limited consulting period in the outpatient department.

Our results might be specific to our hospital, because Yamagata University Hospital is one of the largest hospitals in Yamagata prefecture. Patients with more severe disease are referred to this center from other peripheral hospitals while patients with mild asthma are first diagnosed or treated in their local hospital. Further studies of the prescription patterns in other hospitals should be conducted in order to provide the utmost care and adequate instructions on the use of pharmaceutical products by asthmatic patients.

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