Patterns of bronchodilator therapy in asthmatic outpatients

Toetik Aryani,[1] Riska Kholifatul Rahmawati,[2] Ni Putu Cintyadewi,[3] Arina Dery Puspitasari,[1] Alfian Nur Rasyid,[4] Samirah[1]

[1]Department of Pharmacy Practice, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia; [2]Magister of Clinical Pharmacy Program, Faculty of Pharmacy, Universitas Airlangga, Surabaya Indonesia; [3]Bachelor of Pharmacy Program, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia; [4]Pulmonary Department, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

Abstract

Background: Bronchodilators are used to treat asthma symptoms. The administration of this therapy can be given through monotherapy or in combination to achieve the maximum therapeutic effect.

Objective: This study aimed to examine the prescribing pattern of bronchodilators in asthmatic outpatients

Methods: A retrospective study was done by reviewing and analyzing medical records of asthmatic outpatients from January 2019 until December 2020. Data analysis was performed descriptively.

Results: In this study, bronchodilators were administered by inhalation 97.4% compared to oral routes 2.6%. Combination bronchodilator therapy showed 54.7% compared to monotherapy by 46.3%. The combination ICS/LABA budesonide/formoterol 160/4.5 mcg was the most widely used 45.7%.

Conclusion: The use of a bronchodilator was in accordance with the Global Initiative for Asthma guidelines. The route of drug administration through inhalation is more widely used than oral. Combination bronchodilators were more recommended than bronchodilator monotherapy to control asthma symptoms.

Correspondence: Samirah, Department of Pharmacy Practice, Faculty of Pharmacy, Universitas Airlangga, Surabaya, 60115, Indonesia.
Tel.: +62.315020514
E-mail: samirah@ff.unair.ac.id

Key words: Asthma, β2 agonists, Muscarinic antagonist, Inhaled corticosteroids.

Acknowledgments: The author would like to thank the Universitas Airlangga Hospital, Surabaya.

Contributions: S, substantial contributions to the conception or design research; ANR, consultant of pulmonary, interpretation of data for asthmatic patients; TA, the acquisition, and analysis of data patients; RKR, collecting data on patients; NPC, collecting data on patients; All authors, drafting the research or revising it critically for important intellectual content, and agreement to be accountable for all aspects of the research in ensuring that questions related to the accuracy or integrity of any part of the research are appropriately investigated and resolved. All the authors approved the final version to be published.

Conflict of interest: The authors declare no potential conflict of interest.

Funding: None.

Ethical approval and consent to participate: The research protocols of this study submitted to the Ethics and Law Committee were approved with a certificate number of ethics approval: 140/KEP/2021.

Availability of data and material: Data and materials are available by the authors.

Informed consent: The manuscript does not contain any individual person's data in any form.

Received for publication: 28 December 2022.
Revision received: 5 February 2023.
Accepted for publication: 11 February 2023.

Journal of Public Health in Africa 2023; 14(s1):2533
doi:10.4081/jphia.2023.2533

Introduction

Asthma is a serious global health problem that occurs in all age groups. A survey showed that 300 million individuals worldwide suffer from asthma. The average prevalence is increasing in America, Europe, Africa, and Asia.[1] Specifically, the prevalence of asthma recurrence in all age groups in Indonesia reached (57.5%) in 2018.[2]

Asthma is generally characterized by chronic inflammation of the airways. Global Initiative for Asthma (GINA) guidelines classify asthma severity *i.e.* mild, moderate, and severe based on controller treatment for several months. Mild defined asthma was well controlled with low dose ICS/LABA, moderate when asthma was well controlled with low or medium dose ICS/LABA, severe where asthma remains uncontrolled despite using high dose ICS/LABA or requires high dose ICS/LABA to prevent uncontrolled asthma.[3] The goals of asthma treatment to improve symptoms control, minimize the risk of exacerbations, reduce hospitalizations, prevent side effects from treatment, and achieve normal activities.[4] Inhaled corticosteroids (ICS) are effective as a therapy for controlling asthma symptoms. In uncontrolled conditions even with the use of medium doses of ICS, it is not appropriate to increase the dose of ICS because it can increase the risk of side effects. In addition, using low-dose ICS provides most of the clinical benefits. Rather than increasing the dose, it is necessary to add therapy with a combination to achieve an effective and safe treatment.

Bronchodilators such as β2 agonists and muscarinic antagonists as add-on ICS can improve lung function, control symptoms, and reduce exacerbations.[5] β2 agonist can be combined with ICS if the condition of asthma exacerbation is moderate or severe. Meanwhile, patients with mild asthma can be used β2 agonist and low dose ICS combination when asthma exacerbations occur or

before physical activity that can trigger worsening asthma symptoms.[3] Combination Low dose ICS/long-acting β2 agonist (LABA) are recommended in improving control of symptoms well and preventing exacerbations. In addition, long-acting muscarinic antagonists can be used as adjunctive therapy when the combination of ICS and LABA does not control asthma symptoms well. Meanwhile, a combination short acting β2 agonists (SABA) and ICS are prescribed for relieving symptoms during asthma exacerbations.[3,5]

Bronchodilators widely used to treat asthma were selective β2 agonist agents with an inhalation route of administration. The advantage of the inhalation route of administration is increase the local effect on the smooth muscle of the airway nerves and minimizes the risk of side effects.[6] Selection of the type of bronchodilator and route of administration needs to consider the patient's condition to improve the quality of pharmaceutical care and achieve the maximum therapeutic effect. Therefore, this study examines the prescribing pattern of bronchodilators in asthmatic outpatients.

Materials and Methods

This study used retrospective observation as a research method. It used medical record data of asthmatic outpatients in the pulmonary unit. The samples in this study were all medical record data of stable asthmatic outpatients with bronchodilator therapy at Universitas Airlangga Hospital within 1 year of monitoring therapy from January 2019 until December 2020 period. The research protocols of this study submitted to the Ethics and Law Committee were approved with a certificate number of ethics approval: 140/KEP/2021.

The inclusion criteria in this study were the patient's medical record data from 18-60 years old who had asthma without another comorbid respiratory tract disease and completed at least three visits in one year. Based on data from the Centers for Disease and Asthma Prevention (2019), the prevalence of asthma patients occurs mostly in adults over 18 years old, then to determine the effectiveness of bronchodilators on asthma symptoms control for several months, patients were monitored within 1 year with a minimum of 3 visits. While the exclusion criteria were the patient's medical record data were incomplete, including therapy data for patients who did not receive bronchodilators during one-year therapy monitoring. Data was carried out using a time-limited sampling technique. The number of samples taken in this study obtained was 73 patients.

Eligible medical record data of asthma patients who received bronchodilator therapy from January 2019 until December 2020 were selected. The next step was collecting necessary information from the medical records, such as patient identity, clinical data, laboratory data, and profile of bronchodilator used *i.e.* type of bronchodilator, route of administration, and dosage regiment. The results were analysed descriptively using frequency and percentage.

Results

Table 1 shows the prevalence of asthma was greater in females (80.80%) than in males (19.20%). This study presented the highest of asthmatic patients based on the ages 48-57 years (41.1%). Additionally, this study showed that (76.7%) of asthmatic patients had unknown comorbidities. Meanwhile, asthma patients on bronchodilator therapy do not have any symptoms (41.4%), and (58.6%) still had asthma symptoms such as coughing tightness, chest pain, and shortness of breath. The route of administration through inhalation is the more widely given (97.4%) compared to oral routes (2.6%) showed in Figure 1. Meanwhile, combination bronchodilator therapy showed (54.7%) compared to bronchodilator monotherapy (46.3%) showed in Figure 2.

Table 2 shows the total number of drugs received by 73 asthma

Table 1. Demographic characteristics.

Characteristics	∑ (%) n =73	Total ∑(%)
Sex		
Male	14 (19.20)	73 (100)
Female	59 (80.80)	
Age		
18-27	12 (16.4)	73 (100)
28-37	7 (9.6)	
38-47	19 (26.0)	
48-57	30 (41.1)	
58-60	5 (6.8)	
Comorbid		
Unknown Comorbid	56 (76.7)	73 (100)
Hypertension	10 (13.7)	
Dyslipidemia + Diabetes mellitus	2 (2.7)	
Diabetes mellitus	1 (1.4)	
Hypertension + Diabetes mellitus	1 (1.4)	
Dyslipidemia + Diabetes mellitus + Hypertension	1 (1.4)	
Hypertension + Coronary heart disease	1 (1.4)	
Gastroesophageal reflux disease	1 (1.4)	
Symptoms		
No symptoms	30 (41.4)	30 (41.4)
Cough + tightness	28 (38.4)	43 (58.6)
Cough	9 (12.3)	
Shortness of breath	4 (5.5)	
Cough + chest pain	1 (1.4)	
Cough + shortness of breath + chest pain	1 (1.4)	

patients is 192 drugs because each patient can receive more than one type of bronchodilator drug because the patients get additional therapy when symptoms are not resolved with monotherapy. Some patients have changes in therapy such as decreasing or increasing the frequency of drug administration depending on the evaluation of therapy for each visit. The combination ICS/LABA budesonide/formoterol 160/4.5 mcg was the most widely used (45.7%). In this study, the frequency of budesonide/formoterol 1 inhalation two times daily was the most widely given (32.8%). Meanwhile, another ICS/LABA combination used was fluticasone propionate/salmeterol 250/50 mcg (3.1%). While bronchodilator monotherapy widely used was a SABA fenoterol Hbr dose of 100 mcg (30.7%). The frequency of fenoterol HBr 100 mcg 1 inhalation daily was the most prescribed (10.4%). The results obtained in this study were the types of bronchodilator therapy patterns in all outpatients with asthma without distinguishing the severity level.

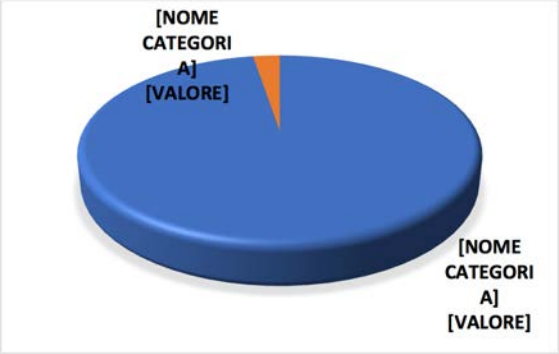

Figure 1. Prevalence of drug administration routes.

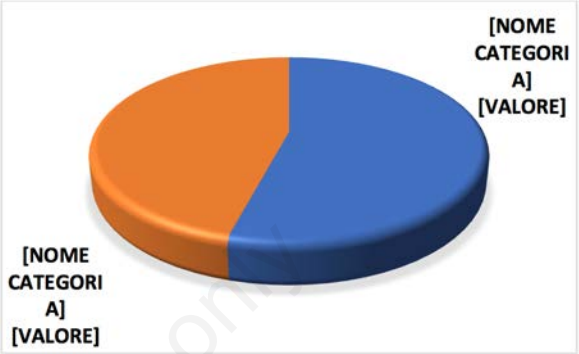

Figure 2. Prevalence receiving monotherapy or combination therapy.

Table 2. Pattern of bronchodilators in ashmathic outpatients.

Drug	Dosage	∑ (%)	Total receiving bronchodilators ∑(%) n=192
β2 agonists			
SABA			
Salbutamol 2,5 mg inhalation	-	9 (4.7)	9 (4.7)
Salbutamol 100 mcg inhalation	100 mcg daily or 1 inhalation daily	2 (1.0)	4 (3.0)
	200 mcg daily or 2 inhalations daily	1 (0.5)	
	100 mcg or 1 inhalation, 2 times daily	1 (0.5)	
	100 mcg or 1 inhalation, 3 times daily	2 (1.0)	
Salbutamol 2 mg oral	2 mg 2 times daily	2 (1.0)	4 (3.0)
	2 mg 2 times daily	1 (1.0)	
	2 mg 3 times daily	1 (1.0)	
Salbutamol 4 mg oral	4 mg 2 times daily	1 (0.5)	1 (0.5)
Fenoterol HBr 100 mcg inhalation	100 mcg or 1 inhalation daily	20 (10.4)	59 (30.7)
	200 mcg or 2 inhalations daily	7 (3.6)	
	100 mcg or 1 inhalation, 2 times daily	14 (7.3)	
	200 mcg or 2 inhalations, 2 times daily	3 (1.6)	
	100 mcg or 1 inhalation, 3 times daily	15 (7.8)	
LABA Procaterol HCl 50 mcg inhalation	-	4 (2.1)	4 (2.1)
Ultra LABA Indacaterol 150 mcg inhalation	150 mcg daily	2 (1.0)	2 (1.0)
Muscarinic Antagonist			
LAMA Tiotropium Bromide 2.5 mcg inhalation	2,5 mcg daily	2 (1.0)	2 (1.0)
Combination			
ICS/LABA Budesonide/Formoterol (160/4.5 mcg) inhalations	1 inhalation daily	16 (8.3)	88 (45.7)
	2 inhalations daily	1 (0.5)	
	1 inhalation, 2 times daily	63 (32.8)	
	2 inhalations, 2 times daily	7 (3.6)	
	1 inhalation, 3 times daily	1 (0.5)	
SAMA/SABA Ipratropium Bromide/Salbutamol (0.5/2.5 mg) inhalations	-	11 (5.7)	11 (5.7)
ICS/LABA Fluticason Propionate/Salmeterol (250/50 mcg) inhalations	1 inhalation, 2 times daily	5 (2.6)	6 (3.1)
	1 inhalation, 1 times daily	1 (0.5)	

Discussion

Table 1 shows the prevalence of asthma was greater in females (80.80%) than in males (19.20%). This finding suggests asthma is related to sex factors. In adults, the prevalence of asthma is higher in females than in males. Ovarian hormones such as estrogen and progesterone increase inflammation in asthmatic patients, while androgens such as testosterones and 5-α dihydrotestosterones reduce inflammation by suppressing innate and adaptive immune system responses.[7] The prevalence of asthma was higher (41.1%) in the age of 48-57 years. The adult, asthma is often caused by exposure to pollutants, cigarette smoke, obesity, and respiratory infections.[8] Additionally, this study showed that 76.7% of asthmatic patients had unknown comorbidities because they were not listed in the medical records. Such absence of data is a limitation of this retrospective study. The prevalence of comorbid hypertension among the outpatients was 13.7%, higher than other comorbidities. Based on pathophysiology, no relationship was found between hypertension and asthma. However, the use of nonselective beta-adrenergic blockers can trigger asthma exacerbations.[9] Good asthma symptoms control status is the goal of therapy *i.e.* reduced or no asthma symptoms, normal activity, no sleep disturbances due to asthma, and optimal lung function.[3] In this study, asthma patients on bronchodilator therapy do not have any symptoms (41.4%), meanwhile (58.6%) still had asthma symptoms such as coughing and shortness of breath. Patients who had no symptoms indicate the therapy is appropriate to control asthma patients. Some of the possibilities for patients having poor asthma control can be related to drug side effects from therapies other than bronchodilators, obesity, lack of physical activity, exposure to allergens or asthma triggers, and lack of emotional control.[3] Additionally, based on the result patients with poor symptoms of asthma such as coughing, tightness, and chest pain were experienced by patients with comorbid coronary heart disease, where the chest pain is one of the symptoms of coronary heart disease.[10]

In Figure 1 bronchodilators are more administered by inhalation (97.4%) compared to oral routes (2.6%). Inhalation routes provide faster onset of action, the greatest local effect on the smooth muscle of the respiratory tract, fewer side effects, and small doses that are more effective than the oral routes.[6] In this study, some patients still received oral drugs with various possibilities, for example. i) inhaled dosage forms are not available; ii) inhalation preparations are more expensive; iii) oral dosage forms are easier to use; iv) administering drugs through oral routes more likely reduces a social stigma than through inhalation; v) most patients still have lack of knowledge regarding inhalation method; vi) in addition, oral preparations can be used in a shorter period.

Combination bronchodilator therapy showed 54.7% compared to monotherapy by 46.3% in Figure 2. Combination more than one bronchodilator in one device provides convenience, improving compliance among patients, and minimizing the risk of side effects.[11] Table 2 shows the combination of budesonide/formoterol 160/4.5 mcg was the most widely used combination of ICS and long-acting β2 agonist (45.7%). The frequency of the combination budesonide/formoterol 160/4.5 mcg varies according to the severity of asthma. In this study, the frequency of budesonide/formoterol 1 inhalation two times daily was the most widely given (32.8%). Another ICS/LABA combination used was fluticasone propionate/salmeterol 250/50 mcg (3.1%). Previous researches found the combination of fluticasone propionate/salmeterol had the same response as the combination of budesonide/formoterol to improve lung function, and both therapies had no difference in the side effects.[12] Long-acting β2 agonist (LABA) formoterol has a rapid onset of action (1-3 minutes after inhalation) with a long duration of action (>12 hours after inhalation).[13] Rapid onset LABA formoterol is as effective as short-acting β2 agonist (SABA) as a reliever, and LABA is more effective than regular SABA. For patients taking SABA and requiring corticosteroids, repeated use of SABA may relieve symptoms temporarily, but giving SABA as a reliever was not more effective in preventing exacerbation than a low-dose combination of ICS/LABA.[3] However, regular use of LABA or SABA potentially decreases the sensitivity of bronchodilators to β agonist or induces tolerance of their bronchoprotective effect, thereby increasing the risk of exacerbations.[3,14]

Using regular LABA or SABA without ICS is not recommended because increases the risk of exacerbation. However, the ICS/LABA combination is effective in improving patient compliance, preventing exacerbations, control of symptoms well, and reducing ICS doses.[3] Additionally, ICS/LABA combination is more able to reduce the incidence of withdrawal lower than ICS monotherapy.[15,16] The role of β2 agonists is vasodilation of the respiratory tract, inhibit the proliferation of respiratory smooth muscles, and become an anti-inflammatory agent.[17]

Short-acting muscarinic antagonist (SAMA) is an alternative therapy to SABA for reducing asthma symptoms.[3] The combination of SABA/SAMA given to asthmatic outpatients was Ipratropium bromide/salbutamol 0,5/2,5 mg amounted to (5,7%). SAMA shows lower effectiveness in providing bronchodilation effects on acute asthmatic patients than SABA.[18] Moreover, SAMA like ipratropium has a slower onset of action than SABA.[3] A clinical study showed that SAMA significantly improved bronchodilation, but it did not improve lung function.[19] However, for adult and paediatric asthmatic patients who had moderate to severe exacerbations. The combination of SABA/SAMA is more likely could improve the peak expiratory flow compared to SABA alone. In addition, this therapy is associated with a lower incidence of hospitalization.[3] Research by Donohue *et al.* showed that the use of a combination of ipratropium bromide/salbutamol provides a better bronchodilation effect and has significantly different in patients with moderate-severe asthma compared to a single salbutamol.[20]

While bronchodilator monotherapy widely used for asthmatic outpatients was a SABA fenoterol Hbr dose of 100 mcg (30.7%) followed by SABA salbutamol 2,5 mg inhalations (4.7%). The dose of salbutamol and frequency of the drug administration varied based on the clinical conditions of the patients. Another type of bronchodilator monotherapy used was the muscarinic antagonist including a Long-acting muscarinic antagonist (LAMA) tiotropium bromide dose of 2,5 mcg given once a day (1,0%). Muscarinic antagonists reduce eosinophils, inhibit the remodelling and thickening of airway smooth muscle.[21] LAMA was an alternative therapy to control asthma as it can optimize lung function and prevent exacerbations better than LABA.[5] Besides, it can be used as adjunctive therapy when the combination of ICS/LABA does not control asthma symptoms well.[3] However, LAMA monotherapy without ICS may increase the risk of exacerbations.[22,23] Several studies have stated that patients who are given LABA in combination with ICS still experience exacerbated symptoms, and thus it is important to consider using a minimally moderate dose of ICS in combination with LABA before adding LAMA.[3,24] Research by Ullah *et al.* showed that the addition of tiotropium in combination ICS/LABA had a significant difference in improving lung function in patients with severe persistent asthma.[25]

Other bronchodilators such as methylxanthines (*e.g.*, theophylline and aminophylline) are no longer used for the asthmatic outpatients in this study. Following GINA guidelines, the administration of methylxanthines is not recommended for the manage-

ment of exacerbated asthma in that methylxanthines have a low safety profile and poor efficacy. Additionally, it has a narrow therapeutic index when it interacts with other drugs. One of the potentially fatal side effects caused by methylxanthines is cardiovascular disorders such as arrhythmia.[26] While compared to SABA, the effectiveness, and safety of SABA are better than methylxanthine.[3]

Research by Lorensia *et al.* showed the incidence of side effects in the use of intravenous aminophylline was very rare and was not even found in several hospital patients in Surabaya.[27]

The results of this study can be used to improve the quality of health services especially in guiding the management of asthma therapy in other hospitals due to combination bronchodilators can improve compliance among patients and minimize the risk of side effects, while inhalation routes bronchodilators provide faster onset of action, the greatest local effect on the smooth muscle of the respiratory tract, fewer side effects, and small doses that are more effective than the oral routes.

Conclusions

Bronchodilators as asthma therapy were used according to the GINA guidelines. The route of drug administration through inhalation is more widely used than oral. Combination bronchodilators were more recommended than bronchodilator monotherapy. The combination of ICS/LABA is the first line to improve lung function, control symptoms, and reduce asthma exacerbations.

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