Bronchodilator Effect of Ipraterol® on Methacholine-Induced Bronchoconstriction in Asthmatic Patients

Kittipong Maneechotesuwan MD, PhD*, Tasneeya Suthamsmai MSc*,
Kanokwan Ratanasaenglert BSc*, Sutat Pipopsuthipaiboon BSc*

** Division of Respiratory Disease and Tuberculosis, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*

Background: *The addition of ipratropium, a synthetic cholinergic antagonist, to β_2-agonist therapy provides an additive improvement in adult with acute severe asthma and COPD because of increased vagal tone in the airways. We asked whether ipratropium in combination with fenoterol (Ipraterol®) improved pulmonary function in comparison with original Berodual®*
Material and Method: *In order to determine the effects of nebulized a single dose of Ipraterol®, the study was conducted in a double-blind, randomized and crossover manner by comparing the effect of nebulized a single dose of Berodual® on methacholine-induced bronchoconstriction. The study consisted of an 1-week run-in phase and two study visits separated by a washout period of 7 days.*
Patients: *We studied 20 patients who ranged from 18 to 80 years of age and had mild to moderate persistent asthma.*
Results: *Nebulized Ipraterol® provided a rapid onset of bronchodilation effect similar to nebulized Berodual® within 5 minutes by significantly increasing FEV_1 from 1.19 L to 1.73 L ($p < 0.001$) and from 1.19 to 1.69 L ($p = 0.0001$), respectively. This effect of Ipraterol® lasted as long (up to 6 hours) and was similar to that of Berodual®. The absolute FEV_1 values at 360 min after Ipraterol® treatment was still higher than the baseline values. We also found that there were no significant differences in the degree of improvement in FEV_1 and hypokalemia following treatment with Ipraterol® and Berodual®.*
Conclusion: *Our data suggest that nebulized Ipraterol offers a statistically significant improvement in pulmonary function without significant systemic absorption causing hypokalemia, with the improvement being comparable to that achieved with nebulized Berodual.*

Keywords: *Asthma, Methacholine, Nebulized bronchodilator, Anticholinergic agent*

J Med Assoc Thai 2011; 94 (Suppl. 1): S66-S71
Full text. e-Journal: *http://www.mat.or.th/journal*

Acute exacerbations of asthma are a common clinical problem with major economic impact[1]. Patients typically present with a variety of manifestrations of worsening airflow obstruction and its consequences, which may be difficult to manage and can be life-threatening[1,2]. In any given year, over 10% of patients with asthma develop at least one severe episode, often requiring attendence at a hospital emergency department[3]. In adults, exacerbations are more common in those with severe, difficult-to-treat asthma[4].

Compared with stable asthma, an acute exacerbation is associated with exaggerated airway inflammation, including recruitment of increased numbers of eosinophils as well as neutrophils[5], and more extensive involvement of smaller distal airways[6,7]. In parallel, there is increased airway resistance, to which distal airway lesions may contribute significantly[8]. Various pathogenetic mechanisms have been invoked to explain the airflow obstruction, including exaggerated bronchoconstriction, airway wall edema, luminal obstruction as a consequence of mucus hypersecretion, and premature airway closure[2,9].

The current management of asthma exacerbation in adults includes regular inhaled bronchodilator therapy, supplemental oxygen, and in most instances, systemic corticosteroids[10]. β_2-agonists are recommended as initial bronchodilating agents[11] whether delivered by nebulizer[12] or by metered dose inhaler with the addition of a spacer device. The addition of anticholinergic agents may also be useful in the early stages of treatment, particularly when asthma is severe, because of increased vagal tone in the airways[13].

Correspondence to:
Maneechotesuwan K, Division of Respiratory Diseases and Tuberculosis, Faculty of Medicine, Siriraj Hospital, Mahidol University, 2 Prannok Street, Bangkok 10700, Thailand.
Phone: 0-2419-7757, Fax: 0-2419-7760
E-mail: sikmn@mahidol.ac.th

Inhaled ipratropium bromide, a synthetic cholinergic antagonist, is the most comprehensively studied of these agents. It has a local anticholinergic effect without significant systemic absorption. Studies of adding ipratropium to β_2-agonists in the treatment of acute asthma have shown greater statistically significant benefits than monotherapy with β_2-agonists alone. Although additional benefit for the combination approach has been shown in adult populations, the published studies have used various combinations of β_2-agonists and anticholinergics and have not always controlled concomitant interventions.

We therefore undertook the present study to compare the bronchodilator efficacy of a fixed combination of nebulized fenoterol (0.5mg) plus ipratropium bromide (0.25 mg) between Ipraterol® and Berodual®. We conducted a double-blind randomized cross-over study to determine time course effects of these bronchodilators on methacholine-induced bronchoconstriction by assessing improvement in FEV_1.

Material and Method

Subjects

Eligible patients were stable and had experienced mild to moderate persistent asthma. None had received a course of therapy with oral corticosteroids within 3 months prior to the study entry. Asthma was diagnosed by the American Thoracic Society criteria. Subjects had a baseline FEV_1 of $\geq$ 50% predicted and demonstrated a reversibility of FEV_1 after therapy with salbutamol (400 μg) of $\geq$ 12% or a provocative concentration of a substance (methacholine) causing a 20% fall in FEV_1 (PC_{20}) of < 4 mg/mL. Exclusion criteria were asthma exacerbation, a respiratory tract infection within 4 weeks before study inclusion, uncontrolled hypertension, hypokalemia, coronary artery disease, and cerebrovascular disease within 3 months before study entry, being pregnant or arrhythmia. Written informed consent was obtained from each patient, and the study was approved by the Ethics Committee of Siriraj Hospital.

Study design

This was a double-blind, randomized, and crossover study using single dose of Ipraterol® and comparative Berodual® on the day of treatment, with a 1-week washout phase between rounds of therapy. Patients entered an initial 1 week run-in period in which anti-asthmatic medications were stopped and short-acting β_2-agonist was used as needed rescue medication until the end of run-in period and throughout washout period. On the study day, patients undertook methacholine challenge test and immediately after the test was ended, the study bronchodilator was administered once via nebulizer. Pulmonary function was then evaluated to determine bronchodilator effect at different time points: 0, 5, 15, 30, 60, 120, 240 and 360 min after nebulization. In addition, serum potassium was determined at 4 hours after the inhalation. The randomized code was withheld from the investigators until completion of the study. The study medication was packed by the central pharmacy according to the randomization code.

Lung function measurement

FEV_1 and FVC were measured using a dry wedge spirometer (Vitalograph, Buckingham, UK). Values are expressed as the percent of predicted normal values. Baseline values were measured after 15 min of rest and were taken as the highest of three readings. Single readings only were taken at other times. Bronchial provocation test results were measured at the study visits. The level of bronchial reactivity was assessed by methacholine challenge, which was performed according to a standardized technique.

To further assess the change in lung function with taking into account the baseline lung function in relation to the patient's optimal lung function (*i.e.*, the potential increase), we used the relative potential improvement (RPI) with some modification as previously described[14]. The change in FEV_1 (FEV_1 at 60 min minus the baseline FEV_1) divided by the potential improvement in FEV_1 (predicted value based on age, sex, height, and race, minus baseline FEV_1):

$$RPI = \frac{FEV_1 \text{ at } t_{60} - FEV_1 \text{ at } t_0}{FEV_1 \text{ (predicted)} - FEV_1 \text{ at } t_0}$$

We then computed the proportion of patients achieving their potential improvement (RPI greater than 20%), and computed the differences in proportion between treatment groups.

Statistical analysis

The results are expressed as mean (SD). Changes in FEV_1 after treatment within group were compared using Wilcoxon signed-rank test. Response to Ipraterol (FEV_1) versus Berodual was assessed by unpaired t-test. Statistical significance was assumed for $p < 0.05$. All statistical testing was performed by

using a two-sided 5% level of significance (GraphPad Prism software; GraphPad Software Inc; San Diego, CA).

Sample size estimation is computed as a non-inferiority study. The FEV_1 after methacholine is 2.7. The FEV_1 at 60 minutes after receiving nebulized Ipraterol® is 3.3 (a difference of 0.6 from baseline FEV_1 after methacholine) and the FEV_1 at 60 minutes after receiving nebulized Berodual® is claimed to be non-inferior to nebulized Ipraterol® when a difference of $\geq$ 0.5 from baseline FEV_1 after methacholine is observed. We accept type I error of 5%, type II error of 20% and a common standard deviation of 0.1. Therefore the number of subject is 14 according to nQuery Advisor 3.0. A total of 24 patients were recruited to ensure that 14 patients completed the study.

Results

Twenty-four patients with asthma were recruited in the present study. 4 patients were excluded because their lung functions were unacceptable. 4 of 20 patients had been treated with β_2 agonists only before study entry. The remaining patients were treated with ICS in the absence or presence of LABA. Demographic data was shown in Table 1.

The mean (SD) of baseline FEV_1 after methacholine challenge in both groups was not significantly different with a value of 1.19 L (0.28) in the Ipraterol® therapy group vs. 1.19 (0.28) in the Berodual® group. There was no significant difference in FEV_1 at the initiation of treatment between the groups including severity of bronchial hyperreactivity (Table 2)

There was significant improvement with the mean FEV_1 in the Ipraterol® group being 1.72, 1.77, 1.83,

Table 1. Demographic data and clinical characteristics of study subjects

Variable	n = 20
Male sex, n (%)	5 (20)
Mean age (years) (SD)	49.3 (12.48)
Median equivalent beclomethasonedaily dose (µg) (IQR)	360.0 (200-725)
Mean FEV_1 (% predicted) (SD)	75.05 (13.36)
Mean FVC (% predicted) (SD)	93.10 (11.79)

Abbreviations: FEV_1, force expiratory volume in second; FVC, force vital capacity; PC_{20}, provocative concentration of a methacholine causing a 20% fall in FEV_1; IQR, interquartile range.

Table 2. Comparison bronchodilation effect of Ipraterol® with Berodual® at each time point

Drugs			Time (minutes)										
		Baseline	-10	0	5	15	30	60	120	240	360	K^+	Geometric mean PC_{20} (mg/ml)
Ipraterol®	Mean FEV_1, L (SD)	1.70 (0.37)	1.19 (0.28)	1.66 (0.44)	1.72 (0.41)	1.77 (0.43)	1.83 (0.41)	1.89 (0.42)	1.89 (0.39)	1.83 (0.38)	1.77 (0.38)	3.75 (0.34)	0.91 (0.51, 1.64)
p-value (compared with T-10)				<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001		
Berodual®	Mean FEV_1, L (SD)	1.67 (0.44)	1.19 (0.28)	1.61 (0.42)	1.69 (0.42)	1.75 (0.42)	1.82 (0.42)	1.86 (0.43)	1.88 (0.44)	1.81 (0.42)	1.78 (0.43)	3.9 (0.34)	1.08 (0.56, 2.15)
p-value*				<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001		
p-value**		0.67	1.0	0.72	0.79	0.91	0.95	0.81	0.97	0.91	0.86	0.14	0.39

Abbreviations: FEV_1, force expiratory volume in second; PC_{20}, provocative concentration of a methacholine causing a 20% fall in FEV_1

* The comparison between FEV_1 at time -10 min (T-10) and other time points as indicated using Wilcoxon signed-rank test.

** The comparison of FEV_1 at each time point after indicated treatments between the groups using unpaired t-test.

1.89, 1.88, 1.83 and 1.77 L at 5, 15, 30, 60, 120, 240, 360 min, respectively (p-values as shown in Table 2) (Fig. 1) when compared with baseline FEV_1 after methacholine challenge at time -10 min. Similarly, there was significant change in mean FEV_1 from baseline in the Berodual® group being 1.69, 1.75, 1.82, 1.86, 1.88, 1.81 and 1.78 L at 5, 15, 30, 60, 120, 240, 360 min, respectively (p-values as shown in Table 2) (Fig. 2). However, delta changes in FEV_1 at each time point were not statistically significant when compared between groups (Table 3).

Comparing differences in proportion defined by RPI showed a benefit of Ipraterol® and Berodual® was 85% and 85%, respectively (p = 1.0) using McNemar test.

Discussion

In this study, we evaluated the short-term efficacy and safety of nebulized Ipraterol® compared with Berodual® for the treatment of methacholine-induced bronchoconstriction mimicking acute exacerbation. Our study demonstrates the efficacy of inhaled Ipraterol® in the treatment of asthmatic patients with methacholine-induced bronchoconstriction. The efficacy of nebulized Ipraterol® and Berodual® for the improvement of airflow rates in a 6 hr period after bronchoprovocation with methacholine was comparable (Fig. 3). The magnitude of improvement in post-bronchodilator FEV_1 after Ipraterol® treatment was comparable to that found in Berodual treatment. Similar to Berodual®, nebulized Ipraterol® had no effect on potassium levels.

Although pathogenetic mechanisms of an asthma exacerbation are associated with exaggerated airway inflammation and airway wall edema, luminal obstruction is a consequence of mucus hypersecretion,

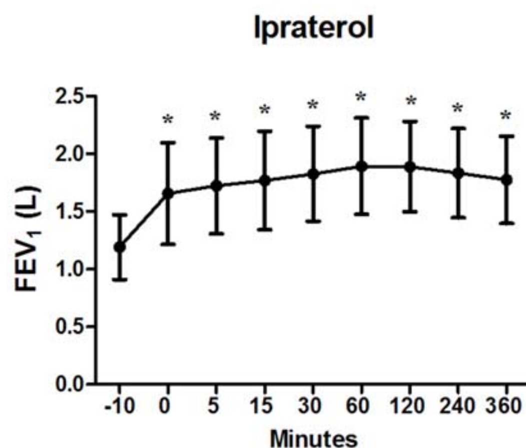

Fig. 1 The time-course effects of Ipraterol on FEV_1. Results 20 patients are expressed as the mean ± SD, * $p < 0.05$.

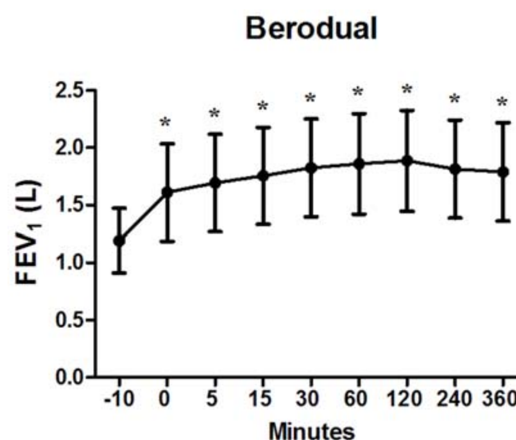

Fig. 2 The time-course effects of Berodual on FEV_1. Results 20 patients are expressed as the mean ± SD, * $p < 0.05$.

Table 3. The magnitude of changes in FEV_1 at each time point after Ipraterol® and Berodual®

Drugs		Time (minutes) 0	5	15	30	60	120	240	360
Ipraterol®	“FEV_1, L (SD)	0.46 (0.25)	0.53 (0.21)	0.58 (0.21)	0.63 (0.20)	0.70 (0.22)	0.69 (0.18)	0.64 (0.21)	0.58 (0.17)
Berodual®	“FEV_1, L (SD)	0.42 (0.22)	0.50 (0.22)	0.56 (0.23)	0.63 (0.22)	0.67 (0.22)	0.69 (0.24)	0.62 (0.21)	0.59 (0.22)
p-value*		0.51	0.61	0.83	0.91	0.65	0.95	0.83	0.83

Abbreviations: FEV_1, force expiratory volume in second; PC_{20}, provocative concentration of a methacholine causing a 20% fall in FEV_1

* The comparison of FEV_1 at each time point after indicated treatments between the groups using unpaired t-test.

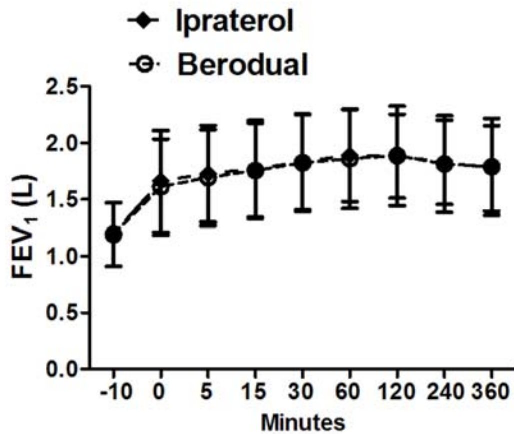

Fig. 3 The comparison between the time-course effects of Ipraterol and Berodual on FEV_1. Results of 20 patients are expressed as the mean ± SD.

and premature airway closure[2,9]. ICS had been withdrawn for 1 week, possibly leading to increased airway inflammation. Our patients were challenged with methacholine to induce bronchoconstriction as shown by evidence that there was a significant decline in FEV_1. This might mimic the pathophysiology of asthma exacerbation in clinical practice. The combination of ipratropium with short-acting β_2 agonist could rapidly reverse methacholine-induced bronchoconstriction and the time-course of Berodual® and Ipraterol® was comparable, suggesting that if Ipraterol® was used in asthmatic patients with an exacerbation, it should provide bronchodilating effect to a similar extent as with Berodual®. We excluded the possibility that differences in bronchial hyperreactivity between Ipraterol® and Berodual® groups were involved in response to these two combination bronchodilator because there was no significant difference in PC_{20} in both groups. We also found no difference in serum potassium levels at 4 hours after treatment with either Berodual® or Ipraterol®.

In summary, Ipraterol® is as effective to treat methacholine-induced bronchoconstriction as Berodual®, without significant changes in potassium levels.

Acknowledgements

We would like to thank Professor Visanu Thamlikitkul for his excellent advice. We thank all patients in this study for their participation.

Potential conflicts of interest

Pharma Innova Co., Ltd Thailand.

References

1. Holgate ST. Exacerbations: the asthma paradox. Am J Respir Crit Care Med 2005; 172: 941-3.
2. McFadden ER Jr. Acute severe asthma. Am J Respir Crit Care Med 2003; 168: 740-59.
3. Robertson CF, Roberts MF, Kappers JH. Asthma prevalence in Melbourne schoolchildren: have we reached the peak? Med J Aust 2004; 180: 273-6.
4. Wenzel S. Severe asthma in adults. Am J Respir Crit Care Med 2005; 172: 149-60.
5. Gibson PG, Norzila MZ, Fakes K, Simpson J, Henry RL. Pattern of airway inflammation and its determinants in children with acute severe asthma. Pediatr Pulmonol 1999; 28: 261-70.
6. Hamid Q, Song Y, Kotsimbos TC, Minshall E, Bai TR, Hegele RG, et al. Inflammation of small airways in asthma. J Allergy Clin Immunol 1997; 100: 44-51.
7. de Magalhaes SS, dos Santos MA, da Silva OM, Fontes ES, Fernezlian S, Garippo AL, et al. Inflammatory cell mapping of the respiratory tract in fatal asthma. Clin Exp Allergy 2005; 35: 602-11.
8. Martin RJ. Therapeutic significance of distal airway inflammation in asthma. J Allergy Clin Immunol 2002; 109: S447-S460.
9. Carroll N, Carello S, Cooke C, James A. Airway structure and inflammatory cells in fatal attacks of asthma. Eur Respir J 1996; 9: 709-15.
10. FitzGerald JM, Hargreave FE. The assessment and management of acute life-threatening asthma. Chest 1989; 95: 888-94.
11. Hargreave FE, Dolovich J, Newhouse MT. The assessment and treatment of asthma: a conference report. J Allergy Clin Immunol 1990; 85: 1098-111.
12. Morley TF, Marozsan E, Zappasodi SJ, Gordon R, Griesback R, Giudice JC. Comparison of beta-adrenergic agents delivered by nebulizer vs metered dose inhaler with InspirEase in hospitalized asthmatic patients. Chest 1988; 94: 1205-10.
13. FitzGerald JM, Grunfeld A, Pare PD, Levy RD, Newhouse MT, Hodder R, et al. The clinical efficacy of combination nebulized anticholinergic and adrenergic bronchodilators vs nebulized adrenergic bronchodilator alone in acute asthma. Canadian Combivent Study Group. Chest 1997; 111: 311-5.
14. Lanes SF, Garrett JE, Wentworth CE 3rd, Fitzgerald JM, Karpel JP. The effect of adding ipratropium bromide to salbutamol in the treatment of acute asthma: a pooled analysis of three trials. Chest 1998; 114: 365-72.

ฤทธิ์ขยายหลอดลมของ Ipraterol® ต่อหลอดลมตีบที่เกิดจากการกระตุ้นด้วยสาร methacholine ในผู้ป่วยโรคหืด

กิตติพงศ์ มณีโชติสุวรรณ, ทัศนียา สุธรรมสมัย, กนกวรรณ รัตนแสงเลิศ, สุทัศน์ พิภพสุทธิไพบูลย์

ภูมิหลัง: *ยาขยายหลอดลมชนิดผสมระหว่าง fenoterol และ ipratropium เช่น Berodual® เป็นยาที่จำเป็นในการรักษาผู้ป่วยโรคหืดและโรคปอดอุดกั้นเรื้อรังในระยะที่โรคกำเริบเฉียบพลันและรุนแรง อย่างไรก็ตามยังไม่มีการศึกษาฤทธิ์ของ Ipraterol® ซึ่งเป็นยาขยายหลอดลมชนิดผสมแบบเดียวกับ Berodual® ต่อภาวะหลอดลมตีบเฉียบพลันในผู้ป่วยโรคหืดในประเทศไทย*

วัสดุและวิธีการ: *เพื่อศึกษาผลของการรักษาด้วย Ipraterol® ชนิดพ่นผ่านหน้ากาก 1 ครั้ง การศึกษาทำในลักษณะ double-blind, randomized, cross-over โดยการเปรียบเทียบกับผลของการรักษาด้วย Berodual® ชนิดพ่นผ่านหน้ากาก 1 ครั้ง ต่อหลอดลมตีบที่เกิดจากการกระตุ้นด้วย methacholine การศึกษานี้ประกอบด้วย run-in phase เป็นเวลา 1 สัปดาห์ และการมาพ่นยาศึกษา 2 ครั้ง ซึ่งถูกคั่นด้วย washout period เป็นเวลา 7 วัน*

กลุ่มผู้ป่วยที่นำมาศึกษา: *ผู้นิพนธ์ศึกษาผู้ป่วยโรคหืดชนิดรุนแรงน้อยถึงปานกลาง จำนวน 20 ราย ที่มีอายุอยู่ระหว่าง 18-80 ปี*

ผลการศึกษา: *ยา Ipraterol® ออกฤทธิ์เร็วภายในเวลา 5 นาทีในการขยายหลอดลมตีบที่เกิดจากการกระตุ้นด้วย methacholine เหมือน กับ Berodual® โดยทำให้ค่า FEV_1 เพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติจาก 1.19 L เป็น 1.73 L ($p < 0.001$) และจาก 1.19 เป็น 1.69 L ($p = 0.0001$) ตามลำดับ และฤทธิ์นี้ของยา Ipraterol® อยู่นาน 6 ชั่วโมงเหมือนกับ Berodual® ค่า FEV_1 ที่เวลา 360 นาทีหลังการรักษาด้วย Ipraterol® ยังคงสูงกว่าค่า FEV_1 พื้นฐาน ผู้นิพนธ์ยังพบว่าไม่มีความแตกต่างในการทำให้ค่า FEV_1 ดีขึ้นและการเกิด hypokalemia หลังจากการรักษาด้วยยา Ipraterol® และ Berodual®*

สรุป: *ข้อมูลของการศึกษานี้แนะนำว่า nebulized Ipraterol® ช่วยทำให้สมรรถภาพปอดดีขึ้นอย่างมีนัยสำคัญทางสถิติโดยปราศจากการดูดซึมของยาเข้าสู่กระแสโลหิตไปทำให้เกิดภาวะ hypokalemia ประสิทธิภาพในการทำให้สมรรถภาพปอดดีขึ้นเท่ากับ nebulized Berodual®*