Is there any difference between effects of ipratropium bromide and formoterol on exercise capacity in moderate COPD patients?

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ÖZET

Orta şiddetli KOAH olgularında ipratropium bromür ve formoterolün egzersiz kapasitesine etkileri arasında fark var mıdır?

Antikolinerjik ilaçlar ile uzun etkili β_2-agonist ilaçların kronik obstrüktif akciğer hastalığı (KOAH)'nda egzersiz kapasitesini iyileştirdiğine dair değişik bulgular vardır. Fakat iki ilacın karşılaştırmalı olarak alındığı çift-kör çalışmalar yeterli sayıda değildir. Bizim bu çalışmadaki amacımız, bu olgularda ipratropium bromür ve formoterolün egzersiz kapasitesine olan etkisini karşılaştırmak ve egzersiz kapasitesi ile fonksiyonel parametreler arasında ilişki olup olmadığını araştırmaktı. Bu çalışma çift-kör, randomize ve iki periyod crossover olarak planlandı. KOAH polikliniğinde takip edilen 10 stabil, gönüllü KOAH olgusu çalışmaya dahil edildi. İlk vizitte tüm veriler kaydedildi. Bir hafta sonra tüm bazal testleri; solunum fonksiyon testleri ve kardiyopulmoner egzersiz testleri yapıldı, daha sonra hastalar iki hafta süreyle günde dört kez 40 µg ipratropium bromür veya günde iki kez 12 µg formoterol kullandı. Bir haftalık ilaçsız periyoddan sonra ilaç bir diğeri ile değiştirildi. Her bir tedavi periyodu sırasında tüm testleri tekrarlandı. Hastalardan dokuzu erkek, biri kadındı ve ortalama yaş 51.1 ± 5.45 yıl idi, tüm olgular ağır sigara içicisiydi, hafif-orta seviyelerde KOAH'ları vardı (FEV_1= %69, FEV_1/FVC= %68). Formoterol ile FEV_1, FEV_1/FVC'de belirgin iyileşme gözlenirken, ipratropium ile FEV_1, FEF_{25-75}, pik oksijen kullanımı ve dakika ventilasyonda düzelme izlendi. Bununla beraber her iki tedavi sonrasında da egzersiz sürelerinde belirgin artışlar izlendi. Her iki ilacın egzersiz kapasitesine ve fonksiyonel parametrelere olan etkileri arasında belirgin fark izlenmedi. Biz bu çalışmada, KOAH'lı olgularda formoterol ve ipratropium bromür tedavilerinin benzer şekilde egzersiz kapasitesinde iyileşmeye neden olduklarını gözledik. Egzersiz kapasitesindeki bu iyileşme FEV_1'deki iyileşme ile oldukça ilişkiliydi.

Anahtar Kelimeler: *KOAH, egzersiz kapasitesi, formoterol, ipratropium bromür.*

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SUMMARY

Is there any difference between effects of ipratropium bromide and formoterol on exercise capacity in moderate COPD patients?

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The effects of anticholinergic agents or long acting β_2-agonists on exercise capacity in chronic obstructive pulmonary disease (COPD) improves various out come measures but there is not enough double-blind study which included comparison of different medications. The aim of this study was to compare the effect of ipratropium bromide and formoterol on exercise capacity and also to determine the relationship between this improvement in functional parameters and exercise capacity for each treatment in patients with COPD. This study was performed as randomized, double blind and two period crossover design. Ten volunteer stable COPD patients were recruited from outpatient COPD clinic. At the initial visit medical data were recorded. One week later baseline measurements; pulmonary function tests and cardiopulmonary exercise testing were performed, afterwards, patients recieved ipratropium bromide 40 µg four times a day or formoterol 12 µg two times a day for two weeks. After a washout period, medications were crossed for another two weeks. After each of tratment period, all tests were performed. Nine subjects were male and mean age was 51.1 ± 5.45 years, all of them were heavy smokers, level of COPD was mild to moderate (FEV_1= 69%, FEV_1/FVC= 68%). While formoterol significantly improved FEV_1, FEV_1/FVC %, ipratropium significantly improved FEV_1, FEF_{25-75}, peak oxygen uptake and minute ventilation. Moreover, both of the medications increased exercise time. There were no differences between effects of ipratropium bromide and formoterol on exercise capacity and functional parameters. We observed that ipratropium bromide and formoterol have similar improvement in exercise capacity in COPD patients. The improvement in exercise capacity also correlated with increase in FEV_1.

Key Words: *COPD, exercise capacity, formoterol, ipratropium bromide.*

Exertional dyspnea is an important feature of chronic obstructive pulmonary disease (COPD) and besides quality of life improvement, alleviation of such symptom is also main therapeutic goals in current guidelines for management of COPD (1). Thus recent studies have suggested anticholinergic agents and long-acting β_2-agonist medications for symptomatic relief and functional improvement insofar as one is able in patients with COPD.

Short-acting, non-selective ipratropium bromide have been using in COPD treatment for so many years and the effects on forced expiratory volume in one second (FEV_1) with exercise capacity have also been demonstrated in so many studies (2-5). The development of inhaled long-acting selective β_2-adrenergic receptor agonist formoterol has represented a useful therapeutic advance for the management of COPD and has been using as an effective alternative to ipratropium bromide for regular treatment (6-8). However there was not enough study about exercise response to the formoterol treatment with COPD patients. Liesker et al. reported that one week maintenance treatment with formoterol and ipratropium bromide had significantly improved lung functions and exercise capacity compared with placebo (5). Finally we could find, two different kinds of bronchodilators were rarely studied at the cross over study in the literature.

The first purpose of this study was to compare the effects of ipratropium bromide and formoterol on exercise performance, which was evaluated by progressive cycle ergometer in patients with COPD and the second purpose was to determine the relationship between the improve-

ment in functional parameters and exercise capacity for each treatment.

MATERIALS and METHODS

This study was a randomized, double-blinded, two period crossover study to determine the effectivity of two weeks treatment with formoterol and ipratropium bromide.

Patient Selection

The patients in this study had COPD as defined by the GOLD updated 2003 criteria (1). Ten volunteer patients with stable COPD were recruited from the private outpatient COPD clinic. All patients signed an informed concent to participate in the study.

Inclusion Criteria

Patients in a stable phase of COPD, whom had assessed by clinical and laboratory findings were enrolled. Also patients had to be free from exacerbation or respiratory infection for at least the past four weeks. Ages were greater than 40 years. All patients had smoking history of at least 10 pack-year; the number of cigarette pack-year was calculated as the product of the period of tobacco use (in years) and the average number of cigarettes smoked per day. Subjects had previous experience with standard pulmonary function testing and the best post-bronchodilator FEV_1 had to be ≤ 80% predicted, with the FEV_1/FVC ratio ≤ 70% predicted.

Exclusion Criteria

Patients who have other pulmonary disease (current or past diagnosis of asthma or atopy) or uncontrolled systemic diseases, such as uncontrolled systemic hypertension, which could contribute to dyspnea or exercise limitation, were excluded. Patients experiencing an exacerbation, requiring systemic corticosteroids or antibiotics, 30 days prior to enrollment were excluded. Participation in a rehabilitation programme for COPD within six weeks prior to enrollment and inability to co-operate to the tests, oxygen desaturation to less than 80% during exercise on room air, were also excluded.

Study Protocol

The study was performed in two steps, at four seperate parts and patients were assesed in five visits. At the initial visit (day 0), participants underwent physical examination and also baseline pulmonary function tests were performed. Medication were arrenged; formoterol and/or ipratropium bromide were quitted but inhaled glucocorticosteroids and methylxanthines were allowed to remain on the treatment protocols. Subjects could use inhaled salbutamol (100 µg/puff) as need as a rescue drug maximum of 8 puffs/day. At the 2nd visit (day 7), baseline pulmonary function tests and a symptom-limited incremental cycle exercise tests were performed. Patients were then randomized and began using the study medication; inhaled formoterol 12 µg or ipratropium bromide 40 µg via a pressurized metered dose inhaler (MDI). After 90 minutes of medication all of the tests were repeated. At the end of the visit nurse told to the subjects to recieve 12 µg formoterol twice daily or 40 µg ipratropium bromide four times a day, for two weeks . At the 3rd visit (day 21), after 90 minutes of the medication subjects performed tests and then medication quited for one week as a wash-out period. At the 4th and 5th visits, after second baseline tests were done, nurse crossed the medication and each procedure repeated step by step as it was in the first period (Figure 1).

Pulmonary Function Tests

Pulmonary function tests (PFT) were performed according to ATS criteria; including spirometric parameters (FEV_1, FVC, FEV_1/FVC% predicted, PEFR, FEF_{25-75}), lung volumes (TLC, FRC, RV, RV/TLC%), single breath diffusion capacity for carbon monoxide (DLCO) and respiratory muscle strength were measured, using “Vmax 229 Pulmonary Function/Cardiopulmonary Exercise Testing Instruments” (SensorMedics, Bilthoven, The Netherlands) in all patients (9). Single breath method was used in the assessment of DLCO. All of the tests were performed in sitting position and the best of three attempts were evaluated. Predicted values were calculated using ECCS reference values (10).

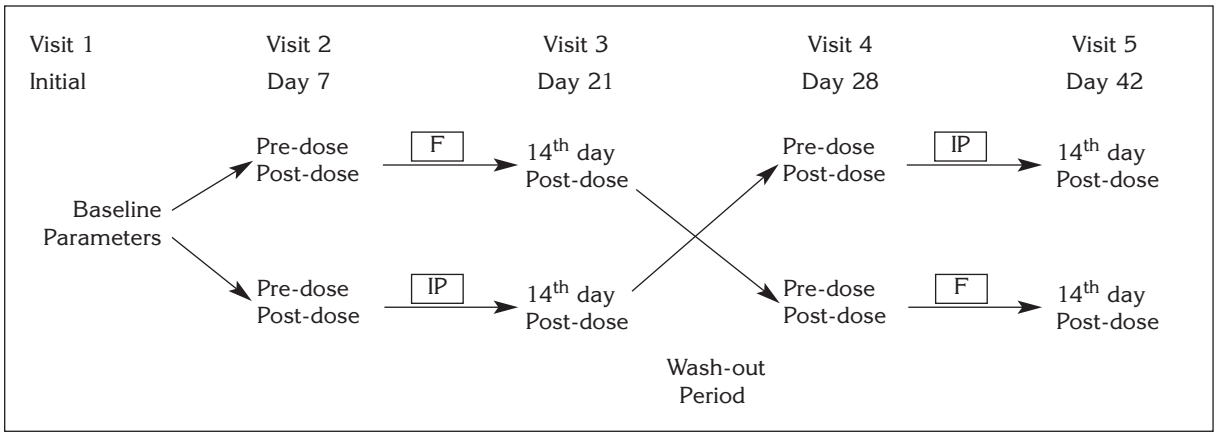

Figure 1. The study protocol illustrates the sequence and timing of visits (F: Formoterol, IP: Ipratropium bromide).

Cardiopulmonary Exercise Testing (CPET)

Progressive cycle ergometer tests to symptom limitation were conducted on an electronically braked cycle ergometer (11) (Vmax 229 Pulmonary Function/Cardiopulmonary Exercise Testing Instruments, Sensor Medics, Bilthoven, The Netherland). All the patients were monitorised continously in terms of ECG, arterial blood pressure, and saturation of oxygen while performing the tests. After the initial evaluation subjects began cycling at a pedalling rate of 40-60 rpm/min for three minutes (warm-up) and afterwards the work was increased by 10-20 watts every minute. The patients were strongly encouraged to perform maximally. The test was terminated at the point of symptom limitation. The reason for ending the test was recorded (i.e. dyspnea, chest pain, leg pain, fatigue or another reason). Peak heart rate (HR), peak work rate (watt), peak oxygen uptake (VO_2), peak oxygen uptake/kg (VO_2/kg), peak CO_2 output (VCO_2), gas exchange ratio (R, VCO_2/VO_2), minute ventilation [VE (BTPS)], tidal volume (VT), respiratory rate (f) were recorded. Metabolic parameters of the exercise test (VO_2 and VCO_2) were compared with predicted normal values of Jones (12).

Arterial Blood Gases Analysis

Arterial blood gas (ABG) analysis were performed at rest and at peak exercise and in room air with a Rapidlab 348 pH/Blood Gas Analyser (Chiron Diagnostics Ltd., Essex, UK). pH, PaO_2, $PaCO_2$, and SaO_2 were measured while breathing on room air.

Safety

Safety was assessed by monitoring adverse events, vital signs, electrocardiography, biochemical and haematological laboratory tests at baseline and at the each step of treatment protocols.

Statistical Analysis

Statistical analyses were done through SPSS (Statistical package for Social Sciences for Windows, SPSS, Inc., Chicago, IL, USA). Results were expressed as means ± SD and p- value of < 0.05 was accepted as significant for all analysis. Data of the value of pulmonary function tests and exercise tests were compared using paired sample students' T tests for crossover treatment protocols. The changes in parameters on 90 minutes (post dose) and 14th day were compared using independent students' t-test. Pearson rank correlation tests were performed to reveal relationships between measured functional parameters and exercise testing parameters.

RESULTS

Patient Characteristics

Ten volunteers were enrolled in the study. All of the subjects completed the study. Male patients were dominant (M/F: 9/1). Ages ranged from 43 to 57 years (mean: 51.1 ± 5.45 years). All of the patients were heavy smokers. Patients had mild or moderate COPD according to GOLD updated 2003 criteria [mean FEV_1 (%): 68.95 ± 10.64 %].

Results of pulmonary function tests and physiological parameters measured at end-exercise are shown in Table 1.

Pulmonary Function Tests

The two treatment sequence groups were comparable at study entry for lung function and exercise capacity. Stability of baseline spirometry at the 1st visit and at the 4th visit, after wash-out period was verified before making inferences from significance test on treatment effects: predose measurement of FEV_1 and FVC were highly repeatable, ensuring that the level of airflow limitation was constant for the duration of study.

Table 1. Baseline characteristics and results of pulmonary function tests and exercise testing.

Parameters	Mean ± SD*
N	10
Male/female	9/1
Age (year)	51.1 ± 5.45 (43-57)
Smoking (pack-years)	47.75 ± 26.50
FEV_1 %	68.95 ± 10.64
FVC %	82.65 ± 10.85
FEV_1/FVC %	68.00 ± 6.60
FEF_{25-75}%	41.40 ± 11.25
TLC %	93.53 ± 12.72
FRC %	95.71 ± 19.45
RV %	121.12 ± 39.19
RV/TLC %	41.59 ± 9.10
IC (L)	2.80 ± 0.62
DLCO (%)	77.89 ± 17.76
Exercise time (min)	7.03 ± 0.73
Work rate (watt)	121.50 ±15.52
VO_2 peak (L/min)	1.21 ± 0.20
VO_2/kg peak (mL/kg/min)	16.75 ± 3.82
VE peak (L/min)	39.86 ± 8.05
HR (/min)	138.42 ± 29.84

* Values are mean ± standard deviation.

FEV_1: Forced expiratory volume in one second, FVC: Forced vital capacity, FEF_{25-75}: Forced expiratory volume 25%-75%, TLC: Total lung capacity, FRC: Functional residual capacity, RV: Residual volume, IC: Inspiratuar capacity, DLCO: Carbon monoxide diffusing capacity, VO_2 peak: Peak oxygen uptake, VO_2/kg peak: Peak oxygen uptake/kg, VE: Minute ventilation, HR: Heart rate.

Formoterol produced statistically significant increase in FEV_1/FVC post-dose and this was maintained after 14 days ($p< 0.05$). Also the increase in mean FEV_1 was similar, both post-dose and after 14 days, however it was just significant after 90 minutes ($p< 0.05$) (Table 2). There was significant improvement in FEV_1 and FEF_{25-75} after post-dose of ipratropium bromide ($p< 0.05$) and maintained at 14th day but the result was not statistically significant (Table 3). Treatment differences and pulmonary function parameters for the formoterol as compared to ipratropium bromide were shown in Table 4. There were no significant differences between ipratropium bromide and formoterol in any of these pulmonary function parameters.

Cardiopulmonary Exercise Testing

All subjects completed the incremental cycle exercise tests at each step of the study. Endurance time was 7.03 ± 0.73 min at baseline. Incremental work at peak ranged 80-145 watt (mean W peak: 121.50 ± 15.52 watt) (Table 1).

Formoterol significantly increased the exercise time, both post-dose and after 14 days ($p< 0.05$). In addition, work rate and VO_2 were increased but the differences were not significant (Table 2). There were similar results with ipratropium bromide in the exercise time, moreover significant increases were reported in the VO_2, VO_2/kg and VE after post-dose but were not maintained at the 14th day (Table 3).

After formoterol, exercise time was increased 0.75 minutes and maintained at the 14th day, the alteration from the baseline was 10%. However the response to ipratropium was 0.90 minutes and at the 14th day alteration from the baseline was 21%. Nevertheless there was no significant difference between the treatment protocols (Table 4).

After each medication, the work rate and VO_2 increased. However it was shown that the differences were not significant. Also each treatment made improvement at IC in each usage but reponses to ipratropium were more than formote-

Table 2. Results of pulmonary functions tests and exercise testing after treatment of formoterol.

	Baseline (mean ± SD)	90 minutes (post-dose) (mean ± SD)	14th day (mean ± SD)
FEV_1 (%)	68.80 ± 11.60	76.60 ± 9.05*	73.20 ± 9.53
FVC (%)	83.50 ± 12.97	87.30 ± 10.51	83.40 ± 6.38
FEV_1/FVC %	67.50 ± 7.53	71.50 ± 6.24*	71.20 ± 6.19**
FEF_{25-75} (%)	42.10 ± 10.18	48.8 ± 16.55	46.40 ± 16.33
TLC (%)	95.43 ± 10.78	93.57 ± 15.75	99.67 ± 17.93
FRC (%)	102.14 ± 16.11	96.14 ±19.26	102.78 ± 30.83
IC (L)	2.76 ± 0.65	3.02 ± 0.68	2.92 ± 0.95
RV/TLC%	41.85 ± 7.66	40.71 ± 5.64	45.44 ± 7.88
Exercise time (min)	7.35 ± 0.47	8.10 ± 0.74*	8.10 ± 1.17**
Work rate (watt)	124.90 ± 12.97	134.40 ± 13.66	134.10 ± 19.67
VO_2 peak (L/min)	1.23 ± 0.26	1.33 ± 0.21	1.32 ± 0.33
VE peak (L/min)	41.46 ± 8.74	44.30 ± 9.41	43.17 ± 7.62

*Difference between baseline and post-dose are statistically significant ($p< 0.05$).
**Difference between baseline and 14th day are statistically significant ($p< 0.05$).

Table 3. Results of pulmonary functions tests and exercise testing after treatment of ipratropium bromide.

	Baseline (mean ± SD)	90 minutes (post-dose) (mean ± SD)	14th day (mean ± SD)
FEV_1 (%)	69.10 ± 10.21	75.00 ± 8.98 *	73.40 ± 16.06
FVC (%)	81.80 ± 8.86	86.00 ± 10.28	85.50 ± 13.56
FEV_1/FVC %	68.50 ± 5.89	70.90 ± 6.88	69.50 ± 7.39
FEF_{25-75} (%)	40.70 ± 12.75	48.20 ± 16.92*	46.40 ± 22.64
TLC (%)	92.85 ± 16.01	96.00 ± 14.89	97.60 ± 18.06
FRC (%)	95.14 ± 23.06	92.29 ± 18.66	97.80 ± 27.07
IC (L)	2.83 ± 0.64	3.03 ± 0.53	3.11 ± 1.0
RV/TLC%	43.71 ± 11.87	42.28 ± 6.78	44.4 ± 10.41
Exercise time (min)	6.70 ± 0.82	7.60 ± 1.17*	8.00 ± 0.94**
Work rate (watt)	118.10 ± 17.82	128.40 ± 19.39	131.10 ± 15.66
VO_2 peak (L/min)	1.18 ± 0.12	1.32 ± 0.17*	1.28 ± 0.18
VE peak (L/min)	38.25 ± 7.37	46.40 ± 7.69*	41.54 ± 7.65

*Difference between baseline and post-dose are statistically significant ($p< 0.05$).
**Difference between baseline and 14th day are statistically significant ($p< 0.05$).

rol, which was insignificant (Table 4). There were FEV_1 and exercise time response to each medication and positive correlation between these parameters were also noticed (To formoterol r: 0.820, $p< 0.01$, to ipratropium r: 0.66 $p< 0.05$) (Figure 2). But there was no significant correlation between post dose IC and exercise capacity (r: 0.44, r: 0.55, respectively).

Safety

There were no adverse events as serious. During ipratropium treatment just a subject suffered from mouth dryness. No significant differences were noted in heart rates before or after exercise in any of the treatment in any patient.

Table 4. Treatment differences pulmonary function and exercise testing parameters for the formoterol as compared to ipratropium bromide.

	Formoterol		Ipratropium bromide	
	90 minutes (post-dose) (mean ± SD)	14th day (mean ± SD)	90 minutes (post-dose) (mean ± SD)	14th day (mean ± SD)
FEV_1 (L)	0.33 ± 0.24	0.20 ± 0.27	0.20 ± 0.22	0.17 ± 0.58
FVC (L)	0.24 ± 0.28	0.07 ± 0.36	0.14 ± 0.34	0.16 ± 0.82
FEV_1/FVC %	4.00 ± 4.92	0.09 ± 0.43	2.40 ± 6.36	0.23 ± 0.41
TLC (L)	-0.13 ± 0.67	0.31 ± 1.21	0.23 ± 0.49	0.32 ± 0.53
FRC (L)	-0.24 ± 0.41	0.16 ± 1.14	-0.06 ± 0.74	0.05 ± 0.64
IC (L)	0.09 ± 0.43	0.16 ± 0.72	0.23 ± 0.41	0.41 ± 0.63
Exercise time (min)	0.75 ± 0.63	0.75 ± 1.06	0.90 ± 1.29	1.30 ± 1.16
Work rate (watt)	9.50 ± 13.75	9.20 ± 18.53	10.30 ± 22.58	13.00 ± 21.60
VO_2 peak (L/min)	0.09 ± 0.15	0.90 ± 0.38	0.15 ± 0.17	0.10 ± 0.17

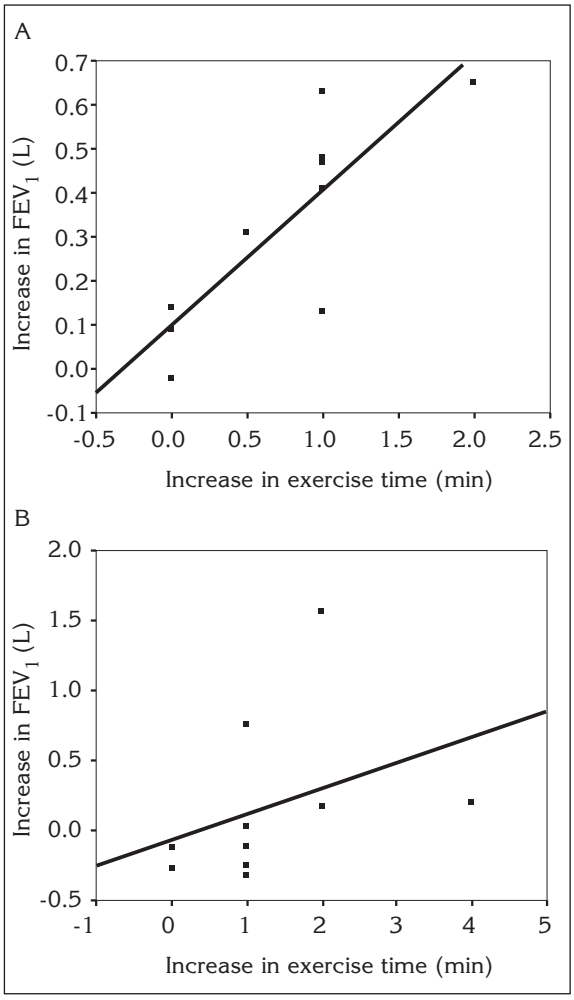

Figure 2. The relationship between increase in exercise time and FEV_1 (A: Formoterol treatment, r: 0.82, B: Ipratropium bromide treatment, r: 0.66).

DISCUSSION

In this study, we observed that the short acting anticholinergic ipratropium bromide and long-acting selective β_2-adrenergic receptor agonist formoterol had similar significant improvements in exercise capacity and pulmonary function in patients with COPD evaluated with incremental cycle exercise tests. This was also associated with an increase in FEV_1 with both medications.

Our results confirm the significant effects of formoterol and ipratropium bromide on pulmonary function parameters in patients with COPD as reported previously. Post-dose of both medications significantly improved FEV_1, while post-dose improvements in FEV_1/FVC and FEF_{25-75} were significant with formoterol and ipratropium bromide respectively and this was maintained at 14th day but the rate of increase was insignificant.

Exercise limitation results are from mechanical factors in COPD patients, but it is not a predominant factor, such as oxygen desaturation during activity, respiratory mechanical disfunction, dynamic compression of the airway during expiration, increased pulmonary arterial pressure many contribute to exercise limitation in COPD (13-17).

One of the main goals of bronchodilator therapy in patients with COPD is to decrease airflow limitation in the airways and, as a consequence

improve dyspnea and exercise tolerance. Studies, which are investigating the effects of bronchodilators on exercise capacity in patients with COPD shows that, just half of the studies determined a significant improvement in exercise capacity. Liesker thinks that this result depends on many factors such as, selection of study population, adequate dose of bronchodilators, number of included subjects in most of the studies was rather small and tests are sensitive to learning effect. As defined in that review, still there is not enough study about the effect of two different types of bronchodilators on exercise performance in COPD patients (18).

Some of the studies determined that COPD patients improved their exercise capacity with ipratropium bromide in an incrimental cycle-ergometer test (5,19,20). Tsukino and Ikeda showed an improvement in exercise capacity with ipratropium bromide by the increase of VO_2max, VEmax, VCO_2max, Wmax (19,20). Also the better effects were defined with the administration of 160 µg or more ipratropium bromide with MDI (20). In that study there was a significant correlation between increase in FEV_1 and exercise capacity improvement. The findings of this study after ipratropium bromide administration were similar and also the present patients had a marked increase in Wpeak and VO_2peak (10%) following the administration of both medications. Moreover there was correlation between the increase in FEV_1 and exercise time.

Liesker et al. determined an exercise time improvement of 0.77 min (7%), after the administration of 80 µg/day ipratropium bromide for one week, which was significantly better than placebo (5). In our study after two weeks of 160 µg/day ipratropium bromide treatment 1.30 min (21%) increase were defined. O'Donnell et al. had administered ipratropium bromide for three weeks time and determined that exercise capacity were significantly improved, on the other hand indirect parameters, which shows reduced lung hyperinflation; IC, IRV and VC were increased, at the same time improvement in dyspnea and exercise endurance were correlated. Also they insist on, an increase of 0.3L in IC was associated with a significant (25%) improvement in exercise endurance time (21). In that study, subjects were moderate to severe COPD patients (FEV_1% 40.0 ± 2.0) and the lung hyperinflation were evident. In our study there was no correlation between IC and exercise capacity. At this point there is a real difference between the study subjects, because our patients were mild to moderate COPD patients and the hyperinflation were not evident (RV: 121%, FRC: 95%). Despite this situation, IC improvements were better after the two weeks treatment of ipratropium bromide.

Liesker et al. studied the three doses of formoterol (4.5 µg, 9 µg, 18 µg b.i.d) and ipratropium bromide (80 µg t.i.d) for one week. All doses of formoterol and ipratropium bromide were increased the lung functions and exercise capacity similarly but Borg dyspnea scores were remained unchanged. Also there was negative dose-response relationship for the three doses of formoterol on the exercise time. Ipratropium bromide effects were similar to formoterol, in administration 4.5 µg, 9 µg dosage (5). In our study both medications effected similarly and significantly on improvement of exercise capacity. Increase in exercise time after the administration ipratropium bromide was longer than the administration formoterol, however the differences were not significant.

Also there are some studies with long acting β_2-agonist, salmeterol. One of these studies showed that there were no significant effect on exercise capacity, evaluated by cycle ergometer and six minute walking distance testing, with the 50 µg b.i.d administration of salmeterol (22). But in another study, Ayers et al. showed that two puffs (42 µg) of salmeterol and four puffs (72 µg) of ipratropium bromide provided similar dyspnea ratings during steady-state exercise. Physiological parameters during exercise were also comparable between the medications, except for a higher IC with salmeterol than with ipratropium bromide. But in that study, this difference in IC did not contribute to a corresponding reduction in breathlessness with salmeterol (23).

In this study, patients had less severe airway obstruction (mean FEV_1= 69%) and the hype-

rinflation were not evident but their exercise performance were limited and breathlessness with exercise were more clear. After the administration of 12 µg formoterol twice daily or 40 µg ipratropium bromide four times a day for two weeks, we observed that each medication had similar improvement in exercise capacity and breathlessness was reduced. There was a correlation between improvement of exercise capacity and increase in FEV_1 but it was not correlated with an increase in IC. We thought that in our patients, who had mild-moderate COPD, limitation of exercise may result from airway obstruction and both medications are usefull to increase exercise tolerance in COPD.

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