The Effect of Salbutamol Controlled Release on Bronchial Hyperresponsiveness in Patients with Bronchial Asthma

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Abstrak

Derajat kepekaan trakeobronkial dapat diukur dengan melakukan uji provokasi bronkus. Makin berat derajat hiperreaktivitas bronkus makin berat serangan asma yang ditimbulkan. Pengukuran kepekaan saluran napas dilakukan menurut cara Cockroft. PC_{20} adalah parameter yang paling sering digunakan untuk menentukan besarnya kepekaan saluran napas yaitu dosis zat inhalasi yang menyebabkan penurunan volume ekspirasi pasca detik pertama (VEP_1) sebesar 20%. Tujuan penelitian ini adalah untuk menyelidiki pengaruh salbutamol lepas terkendali terhadap derajat hiperreaktivitas bronkus. Pada 20 orang penderita asma dewasa diukur besarnya hiperreaktivitas bronkus dengan memberikan provokasi inhalasi larutan metakolin untuk mendapatkan nilai PC_{20} dan PD_{20}. Pemeriksaan dilakukan sebanyak 5 kali yaitu 2 kali pada waktu "run in" dan masing-masing 1 kali setelah 2 dan 4 minggu masa pengobatan serta 2 minggu setelah obat dihentikan. Dari penelitian ini didapatkan PC_{20} meningkat setelah pemberian salbutamol lepas terkendali 4 mg dan 8 mg meningkat dari 1,24 ± 1,51 dan 1,38 ± 1,65 pada waktu "run in" menjadi 1,30 ± 1,18 dan 1,81 ± 1,62 setelah 2 minggu pengobatan serta 1,88 ± 1,58 dan 1,49 ± 1,71 setelah 4 minggu pengobatan. Setelah 2 minggu pengobatan dihentikan nilai PC_{20} pada kedua kelompok menurun menjadi 1,33 ± 1,26 dan 1,29 ± 1,21. Tetapi kenaikan dan penurunan nilai PC_{20} ini secara statistik tidak bermakna. Disimpulkan bahwa pemberian salbutamol lepas terkendali selama 4 minggu pada penderita asma yang diteliti tidak bermanfaat untuk menurunkan hiperreaktivitas bronkus.

Abstract

Bronchial provocation test is a measure of tracheobronchial sensitivity, where the increasing degree of bronchial hyperresponsiveness corresponds to the severity of the asthmatic attack. The method of Cockroft is used to measure the sensitivity of the respiratory tract, and the most frequently used parameter is PC_{20}, which measures the inhalation dose causing a 20% decrease in the expiration volume after the first second (FEV_1). The aim of this study is to investigate the effect of controlled release salbutamol on bronchial hyperresponsiveness. Twenty adult asthmatic patients were provocated by the inhalation of metacholine solution and their bronchial hyperresponsiveness were measured to get the PC_{20} and PD_{20} values. Measurements were conducted 5 times, 2 times at the run in period, once at the 2nd and 4th week of treatment, and once at the 2nd week after treatment. The result of this study showed an increase in PC_{20} in patients treated by 4 mg and 8 mg controlled release salbutamol (1.24 ± 1.51 and 1.38 ± 1.65 at the run in period, were increased to 1.30 ± 1.18 and 1.81 ± 1.62 at the 2nd week of treatment, and to 1.88 ± 1.58 and 1.49 ± 1.71 at the 4th week of treatment respectively). Two weeks after the treatment was stopped, the PC_{20} values of both treatment groups were decreased to 1.33 ± 1.26 and 1.29 ± 1.21. These increase and decrease in PC_{20} values were statistically not significant, so we concluded that a 4 weeks administration of controlled release salbutamol asthmatic patient is not effective in reducing bronchial hyperresponsiveness.

Keywords : *Bronchial provocation test, Salbutamol controlled release, Bronchial asthma*

INTRODUCTION

Asthma is a clinical syndrome, characterized by an increase in tracheobronchial response to various stimuli.[1] This sensitivity is known as bronchial hyperresponsiveness. The major manifestation of bronchial hyperresponsiveness is airway obstruction, and histologically manifested as oedema of the bronchial mucosa, inflamatory cells (especially eosinophil) infiltration, bronchial epithelium damage, and mucous obstruction of the periferal airway.[1,2]

Bronchial hyperresponsiveness is increased considerably by respiratory tract inflamation.[3,4,5] Bronchial inflamation in asthma is a very specific inflamation characterised by massive infiltration of limphocyte and eosinophil to the bronchial mucosa and

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submucosa. Corticosteroids are very effective in inhibiting and reducing the bronchial hyperresponsiveness.[4]

Salbutamol is a β_2 agonist widely used in the treatment of asthma. Various investigators have reported different results about the effect of salbutamol on bronchial hyperresponsiveness.[2,4,5,6,7] In Indonesia, there is no data about the effect of salbutamol controlled release on bronchial hyperresponsiveness.

The aim of this study is to investigate the effect of salbutamol controlled release on bronchial hyperresponsiveness in stable asthmatic patients.

MATERIALS AND METHOD

Twenty adults aged 16-45 years, with chronic asthma, treated in the Persahabatan Hospital, were included in this study.

Inclusion criteria for the study group were: patients with a history of asthma, without other lung disease, heart disease, diabetes mellitus and thyrotoxicosis; not pregnant; having first second forced expiration volume (FEV_1) more than 1000 ml or 65% of the supposed value; 2 months before this study were free from respiratory tract infection, or acute exaxerbation; bronchodilator test showed a 20% increase or more in FEV_1.

The patients were kept from inhalating bronchodilators 10 hours, from taking β_2 8 hours, and from taking slow release theophyline 24 hours before the examination, while the usual doses of corticosteroid were continued.

The lung function and bronchial provocation test were performed on each visit, ie. at the run in period, second and fourth week of treatment, and 2 weeks after the treatment was over. The lung function was tested using a "chest corporation Japan" made, HI 298 microspirometer. The bronchial provocation test was performed using various concentration of metacholine solution as provocating agent. The concentrations of metacholine used were 49 µg/ml, 98 µg/ml, 195 µg/ml, 390 µg/ml, 781 µg/ml, 1.563 µg/ml, 3.125 µg/ml, 6.25 mg/ml, 12.5 mg/ml and 25 mg/ml.

Provocation test according to Cockroft method, was done to measure the PC_{20}, using a 'Japan Chest Corporation' made Astograph TCK 6000 M. First the FEV_1 was measured three times, and the highest value was recorded, followed by the inhalation of control solution (phisiologic salt) for 2 minutes. Thirty and 90 minutes after the inhalation, the FEV_1 was measured again. The test was continued, when the lowest FEV_1 measured after the inhalation of control solution did not differ more than 100 ml compared to the FEV_1 measured before the inhalation. The continuation was done 5 minutes after, by the inhalation of the lowest concentration of metacholin solution (49 µg/ml for 2 minutes), followed by the measurement of FEV_1. Succesive metacholin inhalation using higher concentrations was done, until the decrease of the lowest FEV_1 after inhalation was more than 20% compared to the FEV_1 after the inhalation of control solution. The metacholin dose causing the 20% decrease in FEV_1 was regarded as the PC_{20} (cited from Wiwien et al, 1990).[8]

Measurements of PC_{20} were done 5 times. Four or 8 mg controlled release salbutamol (Volmax ^{R}) was administered twice a day, in the morning and at night, for 4 weeks. Trials were done at random and double blind.

Statistical analysis using 2 way anova and Student's t test was performed to compare the two groups of treatment.

RESULT

Twenty asthmatic patients (10 men and 10 women) aged 16-45 years (mean: 25.2 $\pm$ 8.5 years) were included in this study. The patient's characteristics were shown in table 1.

Eight of the patients were in the 4 mg and 12 were in the 8 mg salbutamol group.

To assess the reproducibility of the PC_{20} value before treatment, bronchial provocation test were done twice at a 2 weeks interval, in the run in period. Statistically, in each group the PC_{20} values of the first and second bronchial provocation test did not differ significantly ($P > .05$).

Statistically, between the 4 and 8 mg controlled release salbutamol groups, there were no significant differences in the PC_{20} values of the first and second bronchial provocation test ($P > .05$).

The PC_{20} values of both bronchial provocation test in the 4 and 8 mg controlled release salbutamol groups were shown in table 2.

The PC_{20} of the first group was 1.24 $\pm$ 1.51 mg/ml and the PC_{20} of the second group was 1.38 $\pm$ 1.65 mg/ml. Statistically, there was no significant difference between the two groups ($P > .05$).

Treatments with 4 mg controlled release salbutamol for 2 weeks increased the PC_{20} values from 1.24 $\pm$ 1.51 to 1.30 $\pm$ 1.18, and treatments with 8 mg increased the values from 1.38 $\pm$ 1.65 to 1.81 $\pm$ 1.62. Statistically, these increases did not differ significantly

(P > .05). From the run in period to the end of 4 mg and 8 mg controlled release salbutamol treatments, there were increases in PC_{20} values from 1.24 ± 1.51 to 1.88 ± 1.58 and from 1.38 ± 1.65 to 1.49 ± 1.71 respectively. Statistically, both increases did not differ significantly (P > .05).

A 4 weeks treatment with 4 mg controlled release salbutamol increased the PC_{20} value to 1.88 ± 1.58, while the treatment with 8 mg decreased the value to 1.49 ± 1.71. Statistically, the PC_{20} values at the 4th week of treatment did not differ significantly from that of the 2nd week of treatment (P > 0.5).

Two weeks after treatment with 4 mg and 8 mg controlled release salbutamol, the PC_{20} decrease to 1.33 ± 1.26 and 1.29 ± 1.21 respectively. Between the 2 doses, statistically the decrease in PC_{20} did not differ significantly (P > .05).

The changes in PC_{20} values, in and after treatment with 4mg and 8 mg controlled release salbutamol were shown in table 3.

Table 1. Characteristics of the patients

Patients number	Age	Sex M/F	Weight	Height	Reversibility (%)	Before treatment	FEV_1			Illness duration
							2nd week of treatment	4th week of treatment	2 weeks after treatment	
1	22	F	45	155	30.9	1680	1760	1680	1480	3 years
2	21	M	64	171	27.5	2360	2570	2840	3050	3 months
3	21	M	45	150	22	2000	1560	1560	1720	11 years
4	24	F	45	150	29.4	1360	1680	1720	1720	15 years
5	21	F	39	153	32.5	1600	2240	2000	2320	2 years
6	24	M	47	164	22.58	1240	2200	2080	2280	2 years
7	36	M	52	166	35	1200	2280	2240	2360	3 years
8	21	F	54	148	21.56	2040	2440	2360	2480	3 months
9	38	F	64	160	38.4	1560	1800	1800	1880	21 years
10	16	M	42	160	20.4	1960	2520	2570	2610	3 years
11	29	M	55	162	34.37	2240	2480	2340	2480	9 years
12	18	M	47	146	26.08	1840	2160	2160	1880	11 years
13	45	F	82	167	23.4	1880	2360	2400	2400	3 months
14	17	F	38	151	36.8	1520	2000	1800	1760	2 years
15	16	F	47	170	25	1600	2260	2000	2160	1 month
16	22	F	48	155	35.48	1240	2440	1760	2160	1 year
17	17	F	67	163	29.2	2360	2810	2710	2890	2 years
18	35	M	67	169	58.82	1080	2610	1080	920	2 years
19	24	M	76	179	21.97	2480	2740	2850	2770	3 years
20	37	M	45	169	43.52	1700	2340	2160	2120	1 year
$\bar{X}$	25.2		53.45	160.4	30.744	1747	2262.	2105.	2172	4.82
SD	8.28		12.11	8.8735	9.05098	406.06	340.4	442.3	497.228	5.60

M = Male, F = Female, FEV_1 = First minute Forced Expiration Volume

Table 2. The reproducibility of bronchial provocation test

Patient	SLT 4 mg		SLT 8 mg		Significancy
	PC_{20} I	PC_{20} II	PC_{20} I	PC_{20} II	
1	2.0	0.42	0.20	0.16	p > 0.05
2	0.34	0.46	0.58	0.39	p > 0.05
3	2.05	4.3	2.10	3.6	p > 0.05
4	1.25	0.76	2.12	3.4	p > 0.05
5	1.4	2.9	0.44	0.43	p > 0.05
6	0.54	0.36	1.9	3.8	p > 0.05
7	1.4	0.67	3.9	3.0	p > 0.05
8	0.23	0.11	0.45	0.46	p > 0.05
9			0.14	0.04	p > 0.05
10			0.22	0.24	p > 0.05
11			0.64	0.25	p > 0.05
12			0.55	0.28	p > 0.05
$\bar{X}$	1.28	1.25	1.10	1.33	
SD	0.81	1.51	1.15	1.57	

Table 3. The change in PC_{20} value

Time	SLT 4 mg			SLT 8 mg			Signi-ficancy
	N	$\bar{X}$	SD	N	$\bar{X}$	SD	
Run in	8	1.24	1.51	12	1.38	1.65	NS
Treatment 1	8	1.30	1.18	12	1.81	1.62	NS
Treatment 2	7	1.88	1.58	12	1.49	1.71	NS
Wash out 1	8	1.33	1.26	12	1.29	1.21	NS
Significancy	F = 0.3 P > 0.05			F = 0.3 P > 0.05			

The mean of PC_{20} values of 4 mg and 8 mg controlled release salbutamol groups altogether in the run in period was 1.30 ± 1.50, in the second week of treatment the mean was increased to 1.53 ± 1.37, while in the 4th week of treatment and 2 weeks after treatment the means were decreased to 1.46 ± 1.63 and 1.29 ± 1.19 respectively. Statistically the increase and decreases in PC_{20} values did not differ significantly (P > .05) from the value of the run in period.

In the 4 mg controlled release salbutamol group, the PD_{20} value (a logaritmic conversion of PC_{20} value) was -0.32 in the run in period; it was increased to -0.04 in the 2nd week and 0.03 in the 4th week of treatment respectively, and at 2 weeks after treatment it was decreased to 0.06. The increase and decrease in the PD_{20} value was statistically non significant (P > 0.05). The same has occured in the 8 mg group, whose PD_{20} value was -0.25 in the run in period, -0.13 and -0.10 in the 2nd and 4th week of treatment, and -0.18 at 2 weeks after treatment. The increase and decrease in the PD_{20} value was statistically non significant (P > .05), as was shown in table 4.

Table 4. The change in PD_{20} value.

Time	SLT 4 mg			SLT 8 mg			Signi-ficancy
	N	$\bar{X}$	SD	N	$\bar{X}$	SD	
Run in	8	-0.32	0.36	12	-0.25	0.60	NS
Treatment 1	8	-0.04	0.38	12	-0.13	0.59	NS
Treatment 2	7	-0.03	0.69	12	-0.10	0.48	NS
Wash out 1	8	-0.06	0.41	12	-0.18	0.56	NS
Significancy	P > 0.05			P > 0.05			

Statistically, there was no significant difference in PD_{20} between the 4 mg and 8 mg controlled release salbutamol groups (P > .05).

The first minute forced expiration volume (FEV_1) value before treatment was 1747 ± 406.06 ml, it was increased significantly to 2262.5 ± 340.4 in the 2nd week of treatment, then decreased to 2105 ± 442.3 ml in the 4th week, and increased again to 2172 ± 497.22 at 2 weeks after treatment. Statistically the decrease in the FEV_1 in the 4th week of treatment and the increase in the FEV_1 at 2 weeks after treatment did not differ significantly from the FEV_1 value in the 2nd week of treatment (P > .05).

In all the patients no serious side effect occured during the bronchial provocation test.

DISCUSSION

The subjects in this study were patients having FEV_1 value more than 1000 ml or more than 65% of the supposed value; this inclusion criterion was used with the aim:

- to avoid the misinterpretation in the FEV_1 value which was decreased after the provocation test. Bronchial provocation test was positive when the FEV_1 value after the provocation was decrease 20% or more. When the initial FEV_1 value was small, decrease of the value caused by the provocation test was difficult to differentiate from the variability of the FEV_1.
- to avoid the subject from heavy airway obstruction, because of the decrease of the FEV_1 after bronchial provocation test. If the initial FEV_1 is low, after the provocation test it will be lower.

In the run in period, reversibility test on all the patients showed that the FEV_1 was increased more than 20% after the administration of a bronchodilator. The purpose of this test was to prove that the subject was an asthmatic patient, so that the effect of treatment to reduce bronchial hyperresponsiveness could be assessed.

In this study we used the bronchial provocation test according to Cockroft method, because this method had a standard and could measure bronchial hyperresponsiveness quantitatively.[9]

This method is often used in the Department of Pulmonology, Faculty of Medicine, University of Indonesia/Persahabatan Hospital.[8,10-13] The metacholine chloride solution as provocative agent is a nonspecific antigen, so that anaphilactic shock will not occur. In the run in period, all the patients in the 4 and 8 mg controlled release salbutamol group were subjected to bronchial provocation test twice. The result was regarded as reproducible when the two provocation test only differed in one concentration of provocative agent.[9] All the patients showed reproducibility in the provocation test, and statistically between the two provocation test the PC_{20} values did not differ significantly. This result means that the test was accurate, and the condition of the patients were stable, and were not in exacerbation state. Most of the patients of the two groups were clasified as having mild (PC_{20} = 2-8 mg/ml) and moderate (PC_{20} = 0.25-2 mg/ml) bronchial hyperresponsiveness, except subject number 8 in the 4 mg, and subject number 1,9 and 10 in the 8 mg controlled release salbutamol group which were clasified as having heavy bronchial hyperresponsiveness (PC_{20} = < 0.25 mg/ml).[9]

Not as the lung function value, the PC_{20} values in the two groups were increased during treatment, but this increase was not significant. After the treatment was stopped, the change in PC_{20} value was also nonsignificant. This result means that this drug has no effect in reducing the bronchial hyperresponsiveness, and this is very much in line with other research which showed that β_2 agonist had no effect in reducing bronchial hyperresponsiveness.[4,6,14,15,16]

In the second week of treatment, in both groups the FEV_1 value was increased very significantly compared to the value before tretment. This means that controlled release salbutamol has good effect to the lung function, but can not reduce the bronchial hyperresponsiveness.

Chung et al[17] showed that salbutamol partly inhibited the bronchoconstriction triggered by platelet activating factor, and had minimal effect in increasing bronchial response after the administration of PAF. This means that 2 agonist does not change the inflamation process in the repiratory tract of an asthmatic patient, and the administration along with glucocortocoid inhalation is recomended, especially when the inhalation of β_2 agonist is required to control the symptoms.[6]

β_2 agonist and theophyllin have no or small effect on bronchial hyperresponsiveness and slow phase asthma.[2,4,6,14] Nevertheless, Davies et al showed that controlled release albuterol increase the median of PC_{20}-FEV_1 before treatment which was 0.153 mg/ml to 0.29 mg/ml after a 12 weeks treatment.[18]

Bel et al studied 12 asthmatic patients and 11 COPD (chronic obstructive pulmonary disease) and reported that 2 agonist reduced the respiratory tract hyperresponsiveness to acute bronchoconstrictor stimulations. Salbutamol increased the FEV_1 acutely to 11.5% of the supposed value in asthma, and to 7.2% in COPD. The increase in PC_{20} was 15 folds in asthma, 5 folds in COPD, and did not have protective effect against heavy respiratory tract obstruction caused by strong stimulation.[7]

Higgins et al[19] reported that the mean of PC_{20} was changed from 0.80 to 4.75 µmol after the administration of salbutamol and from 0.67 to 1.06 µmol after the administration of ipratropiumbromide. The increase in PC_{20} caused by salbutamol was more significant compared to that of ipratropiumbromide (2.26 vs 0.84, $P < .05$).

Bronchial hyperresponsiveness was slightly but significantly increased by longterm (1 year) salbutamol administration.[21,22] The increase in bronchial hyperresponsiveness was not due to subsensitisation of β_2 adrenoceptor to salbutamol, but it was due to the failure of β_2 agonist to inhibit the inflamation process underlying the disease.[21]

Bronchodilators does not interfere with the inflamation process, but it fastly eliminates asthmatic symptoms. Administration of bronchodilators could increase the expose of the respiratory tract to alergens, irritants, and agents in the surroundings of the patient.[22]

During the measurements of bronchial hyperresponsiveness no serious side effect had occured, and this was in line with other findings.[8,10-13]

CONCLUSIONS

1. In the two groups (treated with 4 and 8 mg controlled release salbutamol) the optimal increase in FEV_1 occured in the 2nd week of treatment.
2. Four and 8 mg controlled release salbutamol could increase the PC_{20} and PD_{20} value, but statistically the increase were not significant. This means that

salbutamol does not have effect in reducing bronchial hyperresponsiveness.

3. Measurement of bronchial hyperresponsiveness using metacholine inhalation had no side effect.

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