

Procaterol and Terbutaline in Bronchial Asthma

A Double-Blind, Placebo-Controlled, Cross-Over Study

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Procaterol, a new beta-2 adrenoceptor stimulant, was studied in a double-blind, placebo-controlled, cross-over trial in patients with bronchial asthma. Oral procaterol 50 µg b.d., procaterol 100 µg b.d., and terbutaline 5 mg t.i.d., were compared when given randomly in 1-week treatment periods. The best clinical effect was found with terbutaline. Both anti-asthmatic and tremorgenic effects of procaterol were dose-related. Procaterol appeared effective in the doses tested, and a twice daily regimen would appear to be suitable with this drug.

Key words: beta-2 adrenergic stimulant; bronchial asthma; clinical trial; procaterol; terbutaline.

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The use of beta-2 adrenergic agonists is well established in the treatment of bronchial asthma. The drugs can be given by inhalation, orally, or by injection, and are recommended for prophylactic use as well as during acute exacerbations of the disease.

Procaterol is a selective beta-2 adrenergic stimulant which was synthesized in 1976 (10). The chemical structure is shown in Fig. 1. In animal models of beta-receptor activity, procaterol was shown to be highly selective for beta-2 adrenoceptors (2, 5, 6, 7). Procaterol has a longer lasting bronchodilation than salbutamol in dog and cat (8). The selectivity of each beta adrenergic agonist is, however, dependent on the animal species studied (1), and human studies are essential in evaluating the clinical value in bronchial asthma. The drug has been intensively studied in Japan and has been shown to give a dose-dependent bronchodilatation in patients with bronchial asthma (3, 9). It was found that the duration of the bronchodilatation should allow twice daily administration. The present study was designed to evaluate the clinical effect of orally administered procaterol compared with orally administered terbutaline.

PATIENTS AND METHODS

Twenty-three patients with bronchial asthma were investigated after first being informed of the purpose and nature of the trial. They all showed an improvement of at least 15 % in forced expiratory flow in the first second (FEV₁) 15 min after five puffs from a pressurised aerosol of terbutaline. Twenty-two patients completed the trial. There were 13 men and nine women with a mean age of 51 years (range 18-78) and a mean weight of 68 kg (range 45-97). The mean duration of their disease was 8 years (range 1-52), 15 were considered to have atopic disease and seven were considered non-atopic. Concomitant use of other medications to control asthma was allowed, when kept on a constant daily dose, with the exception of other oral beta-2 adrenergic drugs and oral corticosteroids. All patients had used a beta-2 adrenergic aerosol when needed during the investigational period. Nine patients used theophylline, four patients inhaled corticosteroids, and one patient used cromoglycate.

The trial was designed as a placebo-controlled, cross-over study.

After an initial single-blind placebo period of 7 days, three separate 1-week periods of treat-

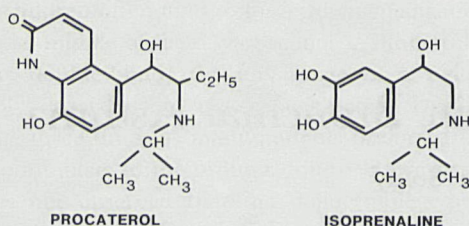


Fig. 1. Chemical structure of procaterol 5-(1-hydroxy-2-isopropylamine) butyl-8-hydroxy carbostyryl. For comparison the chemical structure of isoprenaline is shown.

ment were given in randomized order consisting of one of the following: procaterol 50 µg b.d., procaterol 100 µg b.d., and terbutaline 5 mg t.i.d. By using matching placebo tablets for procaterol 50 µg, 100 µg and terbutaline 5 mg, the three active treatments were given in a double-blind manner.

Each patient kept a diary and recorded peak expiratory flow (PEF) each morning and evening and during the night if wakened because of asthma. Symptom scores (0–3 for each symptom) were recorded separately each morning and evening. The number of beta-2 adrenergic aerosol puffs used were recorded separately for use in daytime and during the night. Side effects were evaluated from the diary where a score (0–3) was given each morning and evening for the subjective discomfort consisting of tremor, palpitation, and nervousness.

Patients were seen at the clinic after each 7-day period and FEV₁ was measured before the morning dose of anti-asthmatic treatment was taken. The patients were asked to assess the severity of asthma symptoms and side effects during the last week in comparison with the previous week, expressed as much better (2), better (1), unchanged (0), worse (–1), or much worse (–2).

The trial was approved by the Ethical Committee of Aarhus. Statistical analysis was performed with non-parametric tests using Wilcoxon's signed rank when comparing the two treatments and Page when evaluating an expected dose-relation between placebo and the two dose levels of procaterol. All tests have been made two-tailed and non-significant differences indicated by NS mean $P > 0.5$.

RESULTS

One patient discontinued the trial after 1 week on placebo because of a severe attack of asthma. The remaining 22 patients completed the 4-week study.

Table 1

Patient preference for the different periods of treatment. The median preference value $\pm$ 95 % confidence limits evaluated from a scale where 2 = much better compared to previous week; 1 = better compared to previous week; 0 = no preference to previous week; –1 = worse compared to previous week; –2 = much worse compared to previous week

	Placebo		Active	
	Week during treatment			
	1	2	3	4
Clinical effect				
Median	0.0	0.4	0.1	0.2
Low	-0.1	-0.1	0.4	-0.2
High	0.1	0.8	0.5	0.7
<i>P</i> *	NS	0.07	NS	NS
Side effects				
Median	0	-0.43	-0.04	0.02
Low	-	-0.09	-0.38	-0.35
High	-	-0.07	0.24	0.43
<i>P</i> *	NS	0.002	NS	NS

* Wilcoxon's signed rank (two-tailed).

Table 2

Patient preference between treatments. The median preference value $\pm$ 95 % confidence limits evaluated from a scale where 2 = much better compared to previous week; 1 = better compared to previous week; 0 = no preference to previous week; –1 = worse compared to previous week; –2 = much worse compared to previous week

	Preference between treatments		
	Placebo–P ₅₀	P ₁₀₀ –P ₅₀	T ₅ –P ₁₀₀
Clinical effect			
Median	0.40	0.15	0.44
Low	–0.08	–0.36	–0.29
High	0.92	0.57	1.07
P^*	0.09	NS	NS
Side effects			
Median	–0.30	–0.29	0.24
Low	–0.65	–0.71	–0.12
High	0.01	0.02	0.77
P^*	0.035	0.034	0.10

* Wilcoxon's signed rank (two-tailed).

The patients' preference for the different periods of treatment is shown in Table 1. Subjectively, the patients felt better during the second week (active treatment) compared with the

first week on placebo ($P = 0.06$), and regarding side effects, placebo was preferred to periods on active drug ($P = 0.002$). In a similar way, the patients' preference for the various treatments

Table 3

Mean values and SEM in the patients' evaluation of effectiveness as determined from diary cards

		Treatment week				Statistical significance
		Placebo	Procaterol 50 µg b.d.	Procaterol 100 µg b.d.	Terbutaline 5 mg t.i.d.	
PER l/min morning	Mean	298	311	298	311	1: NS
	SEM	24	29	25	26	2: NS
PEF l/min evening	Mean	353	351	348	363	1: NS
	SEM	28	29	27	29	2: NS
Asthma severity day	Mean	5.45	4.80	5.00	3.45	1: NS
	SEM	0.93	1.03	1.17	0.84	2: $P = 0.04$
Asthma severity night	Mean	5.35	4.65	4.35	3.55	1: $P = 0.04$
	SEM	0.92	1.15	1.20	0.99	2: NS
Awakening score	Mean	3.35	2.60	2.10	1.70	1: $P = 0.001$
	SEM	0.47	0.50	0.56	0.48	2: NS
Aerosol use day	Mean	16.1	14.7	13.2	12.4	1: NS
	SEM	3.6	3.9	3.2	3.5	2: NS
Aerosol use night	Mean	5.35	3.75	3.75	2.95	1: $P = 0.008$
	SEM	1.17	0.89	1.10	0.98	2: NS

1: Test for: placebo = P_{50} = P_{100} (Page).

2: Test for contrast: $P_{100}-T_5$ (Wilcoxon signed rank two-tailed).

Table 4

Mean values and SEM in the patients' evaluation of side effects as determined from diary cards

		Treatment week				Statistical significance
		Placebo	Procaterol 50 µg b.d.	Procaterol 100 µg b.d.	Terbutaline 5 mg t.i.d.	
Tremor score day	Mean	1.30	3.05	4.15	4.20	1: $P = 0.001$
	SEM	0.78	1.25	1.15	1.26	2: NS
Tremor score night	Mean	1.00	1.60	1.80	1.95	1: $P = 0.02$
	SEM	0.69	0.88	0.94	0.94	2: NS
Palpitation score day	Mean	0.60	0.80	1.05	0.85	1: NS
	SEM	0.24	0.53	0.48	0.37	2: NS
Palpitation score night	Mean	0.30	0.10	0.75	0.20	1: NS
	SEM	0.13	0.07	0.38	0.14	2: NS
Nervousness day	Mean	1.70	2.50	2.35	1.65	1: NS
	SEM	0.92	1.16	1.18	0.94	2: NS
Nervousness night	Mean	1.35	1.80	1.80	1.35	1: NS
	SEM	0.90	1.09	1.06	0.82	2: NS

1: Test for: placebo $\leq P_{50} \leq P_{100}$ (Page).

2: Test for contrast: $P_{100}-T_5$ (Wilcoxon signed rank).

is shown in Table 2. There was a tendency for procaterol 50 µg to be preferred to placebo ($P = 0.09$), whereas no differences were found between the three active test drugs. Regarding side effects, placebo was preferred to procaterol 50 µg ($P = 0.04$) and procaterol 50 µg was preferred to procaterol 100 µg ($P = 0.03$). Data from the patients' daily recordings are shown in Table 3. Analysis of the day-to-day variation of the individual parameters during each week on active treatment did not indicate any carry-over effect. PEF readings showed approximately the same mean values with no significant difference between the 4 trial weeks. The mean morning values ranged from 298 to 311 l/min and the mean evening values from 348 to 363 l/min. The score for severity of asthma was lower on terbutaline than on procaterol and placebo, and this difference was statistically significant during the daytime ($P = 0.04$). Also the frequency of awakening during the night and the day- and night-time aerosol consumption was lower on terbutaline than on the higher procaterol dose. There was a dose-related trend with the highest score on placebo, lower score on procaterol 50 µg, and lowest score on procaterol 100 µg for night-time severity of asthma attacks ($P = 0.04$), number of awakenings ($P = 0.001$), and aerosol consumption ($P = 0.008$).

The evaluation of side effects is shown in Table 4. There was no significant difference between the higher procaterol dose and terbutaline with regard to tremor, palpitation, and nervousness. Tremor showed a dose-related pattern with the lowest score on placebo, higher scores on procaterol 50 µg b.d., and the highest score on procaterol 100 µg b.d., the difference being statistically significant, daytime ($P = 0.001$) and night-time ($P = 0.002$).

DISCUSSION

In a previous study (11) a dose-dependent bronchodilatation was found after a single dose of procaterol, with a concomitant longer duration of action for the higher dose. In addition, a dose-dependency could be demonstrated for the degree of protection given by procaterol to allergen challenges (4).

The present study confirms that procaterol is active in doses of 50–100 µg b.d. Procaterol is 50–100 times more potent on a weight basis compared with terbutaline and salbutamol; this can partly be ascribed to a unique pharmacokinetic profile in that procaterol is absorbed with negligible first pass metabolism.

This study compared a twice daily dose regimen of two dose levels of procaterol with a three times daily regimen of terbutaline tablets. There was no clear patient preference for any treatment period. The effects on asthma symptoms and the tremorgenic effect were dose-related for procaterol. There was a trend towards a lower frequency of awakening during night-time, a lower aerosol consumption, and a significantly lower severity of asthma during terbutaline treatment when compared with procaterol. The above-mentioned effect parameters are assumed to be correlated to some extent. The finding of differences between treatments with P -values of 0.01 or less, should therefore not be ascribed to mass-significance. All three active test drug periods were preferred to the initial placebo period. This suggests that the addition of an oral beta-2 stimulant is of therapeutic value in patients otherwise receiving optimal doses of other anti-asthmatic drugs.

Pulmonary ventilatory function (PEF) was measured just before the morning and evening doses. The finding that there was no difference in these readings during the initial placebo period compared to the active treatment periods, indicates that the duration of the bronchodilatory action of procaterol is no longer than 12 h (b.d. dosage regimen) and no longer than 8 h for terbutaline (t.i.d. dosage regimen).

The side effects noted were few, and mild signs of extrapulmonary stimulation of beta-2 receptors by the drugs were well tolerated. The study shows that procaterol is a potent and selective beta-2 agonist, clinically effective in doses of 50 and 100 µg given morning and evening. Further studies are needed to confirm this, and to evaluate a broader range of procaterol doses, in order to establish guidelines for the effectiveness and tolerability of this new drug.

REFERENCES

1. Brittain, R. T., Farmer, J. B., Jack, D., Martin, L. E. & Simpson, W. T.: Alpha-t-butylaminomethyl-4-hydroxy-m-xylene, -diol (AH.3365): A selective beta adrenergic stimulant. *Nature* 219, 862-863, 1968.
2. Himora, N. & Taira, N.: Assessment of the selectivity of OPC-2009 a new beta adrenoceptor stimulant, by the use of the blood-perfused trachea in situ of the isolated blood-perfusion papillary muscle of the dog. *Br. J. Pharmacol.* 61, 9-17, 1977.
3. Kawai, M. & Maekawa, N.: Efficacy and safety evaluation of procaterol in long-term therapy. *Basic Pharmacol. Ther.* 6, 3626-3636, 1978.
4. Kersten, W., Cremer, G. & Winkler, T.: Protektive Wirkung von Procaterol bei der Allergenprovokation. *Atemw.-Lungenkrkh.* 9, 140-145, 1983.
5. Saitoh, Y., Irie, Y., Hosokana, T., Igana, T., Haskimura, F. & Kohri, H.: Evaluation of a new beta-adrenoceptor agonist, procaterol, based on metabolic responses in rats. *Biochem. Pharmacol.* 27, 2531-2535, 1978.
6. Takayangi, I., Kondo, N., Yamaskita, H., Hongo, T. & Takagi, K.: New selective beta-2-adrenoceptor stimulants 5-(1-hydroxy-2 isopropylaminobutyl) - and 5-(1-hydroxy-2-ethylaminobutyl)-8-hydroxycarboxystyryl hydrochlorides (OPC-2009 and OPC-2030) and cyclic AMP concentration. *J. Pharm. Pharmacol.* 29, 187-189, 1977.
7. Tei, S., Tamaskita, S. & Yabuuchi, Y.: The beta-adrenoceptor stimulant action of procaterol, a new beta-2-adrenoceptor stimulant, on bronchial resistance and heart rate in guinea pigs. *Oyo Yakuri* 17, 335-343, 1979.
8. Yabuuchi, Y., Yamaskita, S. & Tai, S.: Pharmacological studies of OPC-2009, a newly synthesized selective beta adrenoceptor stimulant in bronchomotor and cardiovascular system of the anaesthetized dog. *J. Pharmacol. Exp. Ther.* 202, 326-336, 1977.
9. Yagura, T. & Shida, T.: Effects of a new beta-adrenoceptor stimulating bronchodilator, procaterol, on bronchial asthma after single oral administration; double blind group comparison study at 30 institutions. *Igaku Ko Ayomi* 3, 196-215, 1979.
10. Yoshiaki, M., et al.: Structure and physiochemical properties of procaterol hydrochloride hemihydrate (OPC-2009). *Clin. Rep.* 11, 3804, 1977.
11. Zanetti, C. L., Rotman, H. H. & Dresner, A. J.: Efficacy and duration of action of procaterol, a new bronchodilator. *J. Clin. Pharmacol.* 22, 250-253, 1982.

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