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Ba 679 Br, a new long-acting antimuscarinic bronchodilator: a pilot dose-escalation study in COPD

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ABSTRACT: Preclinical studies with Ba 679 Br have demonstrated a significantly longer duration of action than ipratropium bromide. Following inhalation of single doses, no systemic antimuscarinic effects were noted at doses likely to be bronchodilating in man. The objective of the present pilot-study of Ba 679 Br was to establish the dose-range for its bronchodilatory activity in a small number of chronic obstructive pulmonary disease (COPD) patients, before initiating a formal dose- and time-response study.

Employing an open cross-over design, the efficacy of Ba 679 Br was tested, following single inhalational administration of five doses of increasing magnitude on separate days in six patients with COPD. A piezoelectric crystal was used, in order to nebulize an aqueous solution into a mist suitable for inhalation. There was a mean increase in forced expiratory volume in one second (FEV_1) of 36% 30 min after inhaling ipratropium bromide 40 μg. Pulmonary function tests (FEV_1, and specific airways conductance (sGaw)) were performed, at regular time intervals up to 24 h after test drug inhalation.

The bronchodilatory activity of Ba 679 Br appeared to be dose-related in the dose-range tested (10–160 μg). A peak response was reached in 1.5–2 h, and persisted for 10–15 h in the majority of patients with return to baseline FEV_1 approximately 19 h after dosing. No changes in physical examination, electrocardiogram (ECG) and laboratory safety tests from predose values were noted, and no serious adverse events were reported by the patients.

It is concluded from this preliminary study that Ba 679 Br is an effective, safe and promising antimuscarinic drug, with prolonged bronchodilatory activity in COPD following single dose administration. In order to establish both optimal dose and duration of action, a placebo-controlled study in a larger patient population is now needed.

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The recent development of the new class of long-acting $beta_2$-agonists, *e.g.* formoterol and salmeterol, offers new perspectives for the treatment of asthma. Due to their specific pharmacokinetic and pharmacodynamic properties, these new agents have a prolonged bronchodilatory activity of approximately 12 h [1, 2]. In the treatment of chronic obstructive pulmonary disease (COPD) the antimuscarinic agent ipratropium bromide has acquired and retained a well-defined position over the years [3]. Numerous clinical studies have demonstrated the efficacy and safety of this bronchodilator in patients with COPD. Ipratropium bromide, as the main representative of the new class of antimuscarinics, has important advantages over atropine. It is more bronchoselective and, being a quaternary amine compound, its absorption through the mucous membranes of the respiratory and gastrointestinal tracts is minimal.

Ba 679 Br is the most recently developed antimuscarinic agent and is structurally related to ipratropium bromide (fig. 1). Binding studies with cloned human muscarinic receptors (Hm1, Hm2, Hm3) revealed K_D values in the 10^{-10} M concentration range. In addition, the drug showed "kinetic receptor subtype selectivity" by more rapid dissociation from Hm2 than Hm1 and Hm3. Pharmacological studies in the dog have shown the agent to be highly effective, and especially a long-acting bronchodilator. Its duration of action following inhalation was determined by means of acetylcholine-induced bronchospasms. Ba 679 Br showed a significantly longer duration of protection than an equipotent dose of ipratropium bromide [4]. Moreover, when administered by inhalation to healthy subjects, the substance is free of any systemic effect in dosages likely to be bronchodilating in man.

As no data on its bronchodilator properties in patients were available, it was decided to start with a pilot study, employing an open dose-escalation design, in a relatively small group of COPD patients, before initiating a formal dose- and time-response study.

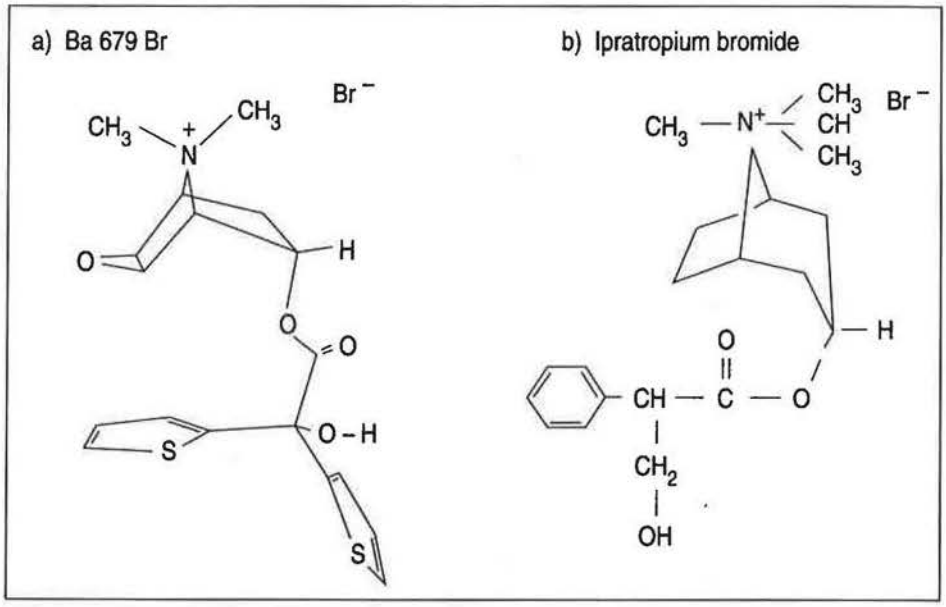

Fig. 1. – Structural formulae of Ba 679 Br (a) and ipratropium bromide (b).

Patients and methods

The objective of the present pilot-study of Ba 679 Br was to establish the dose-range for its bronchodilatory activity in a small number of patients, before initiating a formal dose- and time-response study. This prospective trial was conducted as a unicentre, open, cross-over study with five single inhalational doses of Ba 679 Br of increasing magnitude.

Patients were required to have a diagnosis of chronic obstructive pulmonary disease (COPD), according to the definition of the American Thoracic Society (ATS). On an initial screening visit, the patients had to show a relatively stable, mild to moderately severe airway obstruction with a forced expiratory volume in one second (FEV_1) < 65% of predicted, and FEV_1 < 70% of forced vital capacity (FVC). Predicted normal values were based on the tables for standardized lung function tests of the European Coal and Steel Community. Moreover, patients were required to have a smoking history of more than 10 pack-years, and to be 40 yrs of age or older (females, if postmenopause or surgically infertile). The airway obstruction had to be reversible, as demonstrated by an improvement greater than 15% in baseline FEV_1 30 min after inhalation of ipratropium bromide (metered dose inhaler (MDI) two puffs of 20 μg). Patients with a history of asthma, allergic rhinitis, or atopy, or a blood eosinophil count above 440 per μl were excluded. In addition, patients with any of the following were also excluded from the study: significant cardiac, renal, hepatic, endocrine or metabolic diseases, glaucoma, prostatic hypertrophy or bladder neck obstruction, viral infection or febrile illness, including upper respiratory tract infections during the past month, beta-blocker medication and/or oral corticosteroids.

A wash-out was required for all bronchodilators prior to the start of pulmonary function testing on each test day. Inhaled short-acting bronchodilators were excluded for at least 8 h, long-acting for at least 24 h, oral $beta_2$-adrenergic agonists for 18 h, and xanthines for at least 36 h. Inhaled corticosteroids were allowed if the patient's dosage was stabilized for at least 4 weeks prior to the preadmission visit, and was stable throughout the entire study period.

A piezoelectric crystal (Respimat®) was used to nebulize an aqueous solution of the test drug into a mist suitable for inhalation. The principal element of the Respimat® is an ultrasonic atomizer, consisting of the piezoelectric crystal and a metal plate. An accurately metered dose of 15 μl of the aqueous solution is transferred onto the metal plate of the ultrasonic atomizer. Subsequently, the electrical energy from a battery is converted by the piezoelectric crystal into a vibration, which converts the droplet into a mist, which is inhaled by the patient. The quantity of effective compound per actuation of 15 μl was 10 or 50 μg. Thus, the posology was 1 (10 μg), 2 (20 μg) or 4 actuations (40 μg, 80 μg, 160 μg) on separate days.

The study was performed according to the rules of the declaration of Helsinki, and was approved by the Medical Ethics Committee of the De Wever Hospital, and all patients gave written consent to participate in the study.

Procedure

Prior to admission to the study, a complete medical history, 12-lead ECG and physical examination, including measurement of systolic and diastolic blood pressure and pulse rate, were performed. Baseline laboratory evaluation included blood chemistry, haematology, urinanalysis and total blood eosinophil count, were performed prior and at the end of the study period.

Following the initial screening, patients who qualified were enrolled to receive, initially, three Ba 679 Br doses of increasing magnitude: a low dose (10 μg), an intermediate dose (20 μg), and a high dose (40 μg). The wash-out period between the respective doses was as

follows: a time period of at least 48 h had to elapse between the last observed efficacy of the foregoing dose (defined as $\Delta FEV_1 \geq 15\%$ above predose value) and the administration of the next (higher) dose.

The start of pulmonary function testing (Gould 2800 Autobox, Sensor Medics) on each test day was between 08.30 a.m. and 09.10 a.m. Prior to the test drug and 15, 30, 45, 60 min, 1.5, 2, 3, 4, 6, 8, 10, 12, 15, 19, 23 and 24 h after test drug administration, the flow-volume curve was registered, the airways resistance (Raw) and thoracic gas volume (TGV) measured, and, based on that, the specific airways resistance (sGaw) was calculated. The best value of three (body temperature pressure and saturation (BTPS corrected) was employed. Pulse rate and blood pressure were measured at the same intervals, just prior to pulmonary function testing. The entire study period involved careful monitoring of any adverse events, spontaneously reported or not. Event relationship to study drug was classified as either definite, probable, possible, doubtful, or conditional, according to the guidelines of KARCH and LASAGNA [5]. When, during one of the test days, pulmonary function (FEV_1) deteriorated to such an extent that clinical symptoms of dyspnoea became apparent, the patient was given two puffs of 100 μg salbutamol. Smoking and xanthine-containing food or beverages were not permitted on the test days.

Taking into account the positive results which had been obtained with the dose-range 10–40 μg, and the absence of any drug-related adverse event, it was decided to add two additional test days. On these days, the Ba 679 Br 80 and 160 μg doses were administered to the same patients according to the same procedures as described above, with the exception that on the 160 μg test day pulmonary function tests were performed up to 29 h after test drug inhalation.

Results

Six patients (2 female and 4 male) were enrolled in the study. Their mean age was 52 yrs (range 42–63 yrs), the mean baseline FEV_1 was 1.42 *l* (*i.e.* 46% of predicted normal), and the mean reversibility following ipratropium bromide 40 μg amounted to 36% (table 1). All six patients completed the study. Two patients needed rescue medication (two puffs of 100 μg salbutamol), because symptoms of dyspnoea became apparent during the course of the test day. One of the patients inhaled salbutamol 12 h following the 10 μg dose, whilst a second patient needed rescue medication at 15 h following inhalation of Ba 679 Br 40 μg. This patient appeared to have influenza, which became apparent during the course of the 40 μg test day.

On all five test days, the patients achieved a peak bronchodilation of >15% above their baseline FEV_1, with the exception of two patients receiving the 10 μg dose. The course of the mean bronchodilator responses (FEV_1) expressed as a percentage of the prebronchodilator values is shown in figure 2. Mean predose FEV_1 variability was small (maximally 0.12 *l*, *i.e.* 8%). Following test drug inhalation, the onset of the therapeutic effect was relatively fast from the 20 μg dose onwards. The increase in FEV_1 was already clinically relevant, *i.e.* more than 15%, 15 min after inhalation. The mean peak change in FEV_1 of 21% (10 μg), 30% (20 μg), 32% (40 μg), 47% (80 μg) and 43% (160 μg) was found 1.5–2 h after dosing. In table 2 the increase in FEV_1 obtained with the different doses of Ba 679 Br at 30 and 60 min after inhalation, is compared with the reversibility 30 min following 40 μg of ipratropium bromide.

With the highest test doses (Ba 679 Br 80 and 160 μg), the FEV_1 responses after 30 min were somewhat lower than following ipratropium bromide inhalation, whereas the effects of Ba 679 Br 80 μg and 160 μg after 60 min were higher. In this respect, it is emphasized that a direct comparison between both drug effects is hampered by the fact that an aqueous solution of the test drug Ba 679 Br was nebulized into a mist suitable for inhalation, whilst ipratropium bromide was administered *via* a metered dose inhaler. The degree of bronchodilation following Ba 679 Br was dose-dependent up to a dose of 80 μg, which seemed to be the optimum dose.

It appeared that there was still an improvement of 20% in baseline FEV_1 12 h after inhalation of the 80 and 160 μg doses. The baseline FEV_1 was reached approximately 19 h after dosing. The reduced duration of the effect observed following the 40 μg dose can be explained by the less satisfactory results in the patient who met the

Table 1. – Characteristics of patients

Patient no.	Sex	Age yrs	Disease duration yrs	Height cm	Weight kg	FEV_1 predicted *l*	FEV_1 baseline *l*	FEV_1 % predicted	Reversibility* post *l*	Reversibility* % change from baseline
1	F	48	30	144	50	1.92	0.98	51	1.30	33
2	M	42	25	177	100	3.94	1.68	43	2.58	54
3	M	62	28	178	95	3.36	1.62	48	2.19	35
4	F	63	44	169	75	2.55	1.26	49	1.91	52
5	M	51	23	174	70	3.57	1.76	49	2.23	27
6	M	48	9	174	65	3.65	1.23	34	1.42	15
Mean		52	27	169	76	3.16	1.42	46	1.94	36
Median		50	27	174	73	3.46	1.44	49	2.05	34

*: following two puffs of 20 μg ipratropium bromide; FEV_1: forced expiratory volume in one second.

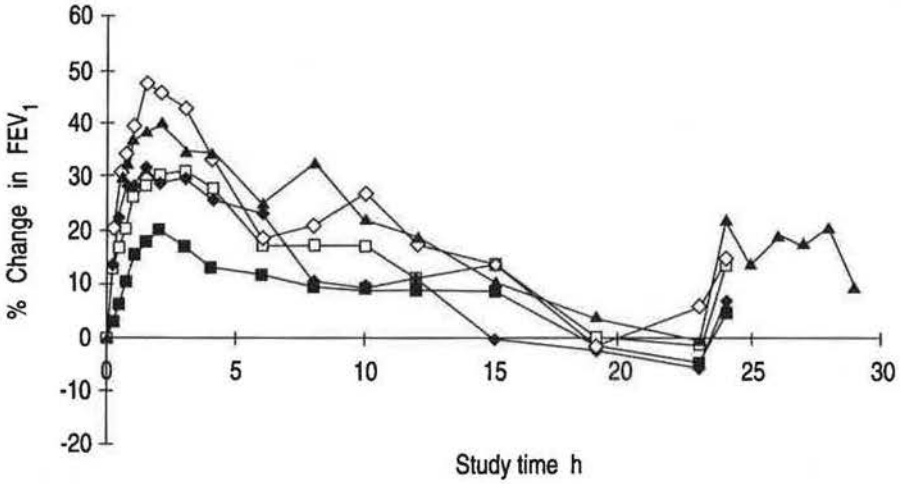

Fig. 2. – Percentage change in FEV_1 (*l*) from baseline for Ba 679 Br 10, 20, 40, 80 and 160 μg. —■— : 10 μg (baseline 1.43 *l*); —□— : 20 μg (baseline 1.39 *l*); —◆—: 40 μg (baseline 1.39 *l*); —◇—: 80 μg (baseline 1.31 *l*); —▲—: 160 μg (baseline 1.41 *l*). FEV_1 forced expiratory volume in one second.

criteria on that test day, but who displayed the first symptoms of what appeared to be influenza during the course of the day.

An early morning dip in bronchodilation was followed by a marked return above the baseline FEV_1 at 24 h (*i.e.* 09.00 a.m.) after test drug inhalation. In order to assess the bronchodilatory activity beyond this time-point of measurement, on the 160 μg test day the pulmonary function tests were continued up to 29 h after dosing. As shown in figure 2, the mean FEV_1 initially dropped at 19 and 23 h, but increased again to approximately 20% above baseline FEV_1 in the time period 24–28 h, and, subsequently, to 10% at 29 h after inhalation. Since in this pilot-study no proper placebo test day was included, patients were requested to withdraw their bronchodilator therapy for a sufficient time period, and to come to the clinic early in the morning in order to assess their baseline FEV_1 at 09.00, 10.00 and 11.00 a.m. These results are displayed in figure 3. There appeared to be a negligible increase in FEV_1, as could be expected on the basis of the circadian variation in pulmonary function. However, this physiological increase in FEV_1 is significantly smaller than the FEV_1 response observed following inhalation of Ba 679 Br 160 μg.

The bronchodilator response expressed as a percentage of the initial (prebronchodilator) FEV_1 is more dependent on the initial FEV_1 than the response expressed as a percentage of the predicted normal FEV_1 [6]. Evaluation of this mode of expression confirmed the findings, as described above, for the bronchodilator response expressed as a percentage of baseline FEV_1.

Figure 4 shows the mean increase in sGaw as a function of time post test drug inhalation, expressed as percentage of the predose sGaw value. Evaluation of this parameter showed a similar dose-dependent bronchodilatory response to that observed with the FEV_1. Following the 80 μg dose, a continuous effect was observed for more than 24 h. At the end of the 160 μg test day one patient showed the first symptoms of a bronchial infection, which is mainly reflected in the sGaw measurements. This explains the discrepancy observed between the FEV_1 and sGaw

Table 2. – FEV_1 responses following inhalation of Ba 679 Br

Patient No.	IpBr*	Test drug Ba 679 Br									
		10 μg		20 μg		40 μg		80 μg		160 μg	
	30 min	30 min	60 min	30 min	60 min	30 min	60 min	30 min	60 min	30 min	60 min
1	33 (17)	13 (6)	17 (8)	22 (11)	33 (17)	20 (9)	30 (15)	41 (18)	38 (17)	44 (23)	54 (29)
2	54 (23)	-2 (-1)	4 (2)	10 (4)	19 (7)	27 (10)	29 (11)	23 (11)	28 (14)	32 (18)	27 (15)
3	35 (17)	11 (5)	39 (17)	27 (12)	46 (20)	43 (19)	43 (19)	46 (17)	56 (21)	53 (20)	58 (22)
4	52 (25)	12 (6)	15 (7)	26 (13)	29 (14)	16 (9)	25 (13)	32 (15)	44 (21)	11 (6)	21 (12)
5	27 (13)	12 (6)	20 (10)	11 (6)	16 (8)	16 (9)	20 (11)	26 (10)	48 (19)	19 (7)	35 (13)
6	15 (5)	-6 (-2)	-1 (0)	7 (3)	17 (6)	20 (5)	23 (7)	25 (8)	30 (9)	31 (10)	40 (12)
Mean	36 (17)	7 (3)	16 (7)	17 (8)	27 (12)	24 (10)	28 (13)	32 (13)	41 (17)	32 (14)	39 (17)
Median	34 (17)	12 (6)	16 (8)	17 (9)	24 (11)	20 (9)	27 (12)	29 (13)	41 (18)	32 (14)	38 (14)

Data are expressed as a percentage change from the predose FEV_1 (and in parenthesis the change is given as a percentage of the predicted normal FEV_1). *: two puffs of 20 μg ipratropium bromide (IpBr) from a metered dose inhaler. FEV_1: forced expiratory volume in one second.

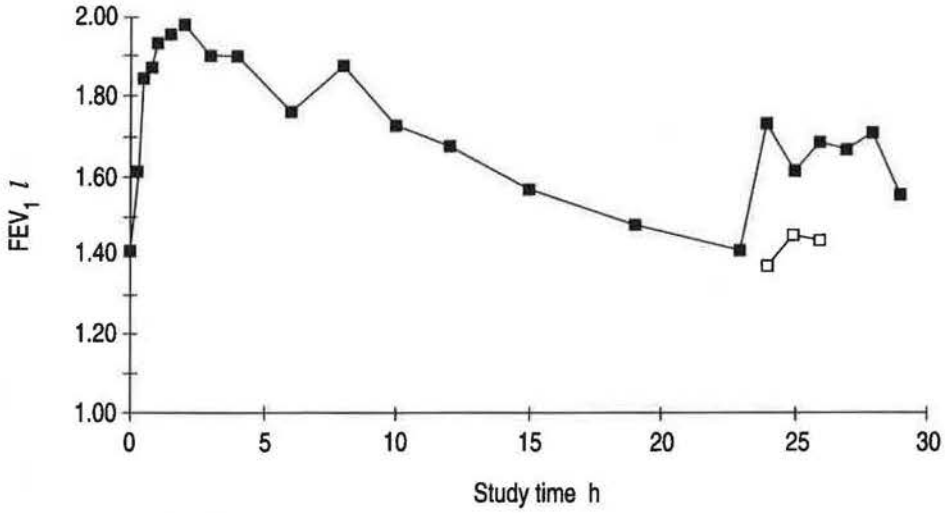

Fig. 3. – FEV_1 time-response curve for Ba 679 Br 160 µg and baseline FEV_1 values at 09.00, 10.00 and 11.00 am. —■— : 160 µg; —□— : "baseline". FEV_1: forced expiratory volume in one second.

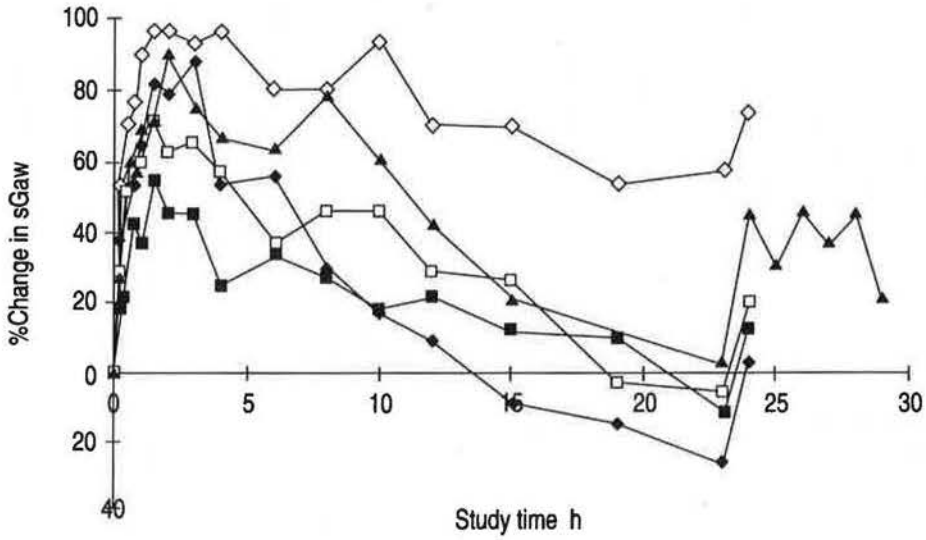

Fig. 4. – Percentage change in sGaw ($s^{-1} \cdot kPa^{-1}$) from test day baseline for Ba 679 Br 10, 20, 40, 80 and 160 µg.—■—: 10 µg (baseline 0.33 $s^{-1} \cdot kPa^{-1}$); —□—: 20 µg (baseline 0.35 $s^{-1} \cdot kPa^{-1}$); —◆—: 40 µg (baseline 0.34 $s^{-1} \cdot kPa^{-1}$); —◇—: 80 µg (baseline 0.30 $s^{-1} \cdot kPa^{-1}$); —▲—: 160 µg (baseline 0.33 $s^{-1} \cdot kPa^{-1}$). sGaw: specific airways conductance.

data on the 80 µg and 160 µg test days. Similar to the FEV_1 findings, the baseline sGaw was reached approximately 19 h after dosing, whereas the results of the 40 µg test day were again slightly more negative, due to influenza in one patient.

No systemic anticholinergic adverse effects were reported by the patients. With respect to the physical examination, blood pressure, pulse rate, ECG and laboratory tests, no changes from predose values were noted.

Discussion

In an open, cross-over design the bronchodilatory activity of Ba 679 Br was assessed following inhalation of single doses of increasing magnitude.

Following an initial screening visit, the patients selected were initially enrolled to receive three doses of the test substance a low dose (10 µg), an intermediate dose (20 µg), and a high hose (40 µg) respectively. Since these doses had been selected on the basis of pharmacological studies and safety data obtained after the first application of Ba 679 Br to healthy subjects, it was decided, not to include a proper placebo test day in the present pilot-study to avoid overburdening the patients. In this respect, it is emphasized that the present scheme of pulmonary function testing already made very high demands both on the participating patients and on the pulmonary function technicians.

Evaluation of the pulmonary function data, obtained in the dose-range 10–40 µg, revealed the prolonged activity of Ba 679 Br in man. Since the magnitude of the

bronchodilatory response appeared to be dose-related, no adverse events had been noted and, moreover, the maximum bronchodilatory response seemed to be less than the response seen after ipratropium bromide, it was decided to extend the pilot-study with two additional doses, *i.e.* Ba 679 Br 80 and 160 μg.

Reviewing all pulmonary function data acquired in a dose-range of 10–160 μg, the conclusion seems to be justified that Ba 679 Br 80 μg produced the maximum bronchodilatory response in the present small group of six patients with a documented diagnosis of COPD. The mean peak increase in FEV_1 of 47% was reached 1.5 h after inhalation. However, as early as 15 min after inhalation, a mean increase of 23% above baseline FEV_1 was found, indicative of a rapid and clinically relevant bronchodilatory effect.

Moreover, the findings of the preclinical pharmacological studies with respect to the duration of action were confirmed in man, since effect (*i.e.* ΔFEV_1 above the 15% level) lasted for a mean of 15 h. The long-acting bronchodilator effect was confirmed by the sGaw data. FEV_1 returned to baseline approximately 19 h after dosing, and increased again markedly above baseline at 24 h. In the first phase of the present pilot-study, when the lower dosages (10, 20 and 40 μg of Ba 679 Br) were administered, this "spontaneous" rebound of the FEV_1 at 24 h had already been observed. Consequently, the pulmonary function testing was continued for a period of up to 29 h after inhalation of the 160 μg dose. A return above the baseline FEV_1 and sGaw of approximately 20% was seen in the time period 24–28 h after dosing.

How should this second peak of bronchodilatory response be interpreted and, furthermore, to what extent is the bronchodilatory effect of Ba 679 Br affected by the circadian variation of airway responsiveness? Several factors, such as circadian variation in concentrations of circulating adrenaline and cortisol, together with a nocturnal increase in vagal tone [7–9], may be involved. In order to obtain a better insight into the observed phenomenon of a second peak response, it would be useful to assess the bronchodilatory response following Ba 679 Br administration in the evening (*e.g.* 9.00 p.m.), so that the plateau of the bronchodilatory effect on bronchial obstruction coincides with the normal daily variation of the bronchial tonus.

The present pilot dose-escalation study of Ba 679 Br has clearly demonstrated its bronchodilatory activity, which appeared to be dose-related in the dose-range tested (10–160 μg). It is, therefore, warranted to initiate an optimally designed formal dose- and time-response study, especially taking into account the required scheme for pulmonary function testing.

It is concluded that Ba 679 Br is an effective, safe and promising antimuscarinic drug, with prolonged bronchodilatory activity in COPD following single dose administration. However, in order to establish both optimal dose and duration of action, a placebo-controlled study in a larger patient population is needed.

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