Eur Respir J
1993, 6, 181–188

Bronchial responsiveness to inhaled propranolol in asthmatic children and adults

A. Foresi, A. Chetta, A. Pelucchi, B. Mastropasqua, D. Moretti, D. Olivieri

Bronchial responsiveness to inhaled propranolol in asthmatic children and adults. A. Foresi, A. Chetta, A. Pelucchi, B. Mastropasqua, D. Moretti, D. Olivieri.

ABSTRACT: Inhaled propranolol (P) was administered to a population which included asthmatic children (30 subjects) and adults (43 subjects): 1) to investigate the determinants of induced bronchial response; 2) to examine the relationship with treatment requirements; 3) to determine the relationship with responsiveness to methacholine (M) and ultrasonically nebulized distilled water (UNDW) (50 subjects); and 4) to establish the short-term repeatability of bronchial response to propranolol compared with methacholine (22 subjects). Bronchial response to propranolol and methacholine was expressed as the cumulative provocative dose (PD_{20} in μmol) and responsiveness to UNDW as the provocative output (PO_{20} in $ml \cdot min^{-1}$) producing a 20% fall in forced expiratory volume in one second (FEV_1).

Response to propranolol was significantly related to the degree of responsiveness to methacholine, but not to age, gender, presence of atopy, age at asthma onset, or baseline FEV_1. $PD_{20}P$ was measurable in all but three subjects. A significant difference in mean $PD_{20}M$ but not in $PD_{20}P$ was found between subjects requiring more anti-asthmatic treatments compared to those without therapy. The difference between geometric mean $PD_{20}P$ and geometric mean $PD_{20}M$ was 14.1. $PO_{20}UNDW$ was measurable in only 21 out of 50 subjects. Both $PD_{20}P$ and $PD_{20}M$ were significantly lower in responders to UNDW than in nonresponders. Reproducibility of $PD_{20}P$ was comparable to that of $PD_{20}M$ (coefficients of repeatability: 1.17 and 1.09).

We conclude that bronchial responsiveness to propranolol is safely measurable in most children and adults with asthma. Repeatability of bronchial response to propranolol is comparable to that of methacholine. Moreover, responsiveness to propranolol is not a predictor of treatment requirement. In general, inhaled propranolol is a less potent bronchoconstrictive drug than methacholine. Although, responsiveness to propranolol seems to reflect the degree of nonspecific bronchial hyperresponsiveness, bronchial sensitivity to methacholine did not predict that to propranolol.

Eur Respir J., 1993, 6, 181–188.

Servizio di Broncopneumologia e Fisiopatologia Respiratoria "G. Campari", Ospedale Città di Sesto San Giovanni, Milano and Istituto di Clinica delle Malattie dell'Apparato Respiratorio, Ospedale Rasori, Università di Parma, Parma, Italy.

Correspondence: D. Olivieri
Istituto di Clinica delle Malattie
dell'Apparato Respiratorio
Università di Parma
Viale Rasori 10
43100 Parma
Italy

Keywords: Asthma
bronchial challenge
methacholine
propranolol
ultrasonically nebulized distilled water

Received: October 11 1991
Accepted after revision July 25 1992

Several studies have shown that β-adrenoceptor blocking drugs, administered orally, parenterally, or locally (by inhalation or instillation), cause bronchoconstriction in asthmatics but not in normal individuals [1–12]. Comparative studies have established that this bronchial effect was related to the β-blocking potency and selectivity of the drugs [13, 14]. These early studies also suggested that induced bronchoconstriction was more pronounced in more severe asthma [2, 15]. Recently, it has been demonstrated that dl-propranolol hydrochloride (P) can be safely administered by inhalation in a stepwise manner [15–19], and that it induces a dose-dependent bronchoconstriction [17–19]. However, clinical and physiological factors which influence bronchial responsiveness to propranolol in asthmatic patients are poorly understood. Presence of atopy was associated with a higher prevalence of a significant response to propranolol [16], and the degree of bronchial responsiveness was not related, or only poorly related, with baseline forced expiratory volume in one second (FEV_1) [19]. In addition, very few studies, including small groups of subjects, have been addressed to determining the short-term reproducibility of bronchial response to inhaled propranolol [17, 18].

The development of bronchoconstriction after β-adrenergic blockade in asthma has been considered a feature of the presence of bronchial hyperresponsiveness [20]. But, in some asthmatic patients, no significant bronchial response has been reported after inhaling propranolol [16, 19]. In addition, bronchial responsiveness to inhaled propranolol is not related [17, 18, 21], or is rather poorly related [19], to bronchial responsiveness to a direct stimulus, such as methacholine (M), or to an indirect stimulus, such as histamine. So far, the relationship between propranolol

responsiveness and responsiveness to a non-pharmacological stimulus, such as ultrasonically nebulized distilled water (UNDW), has not been investigated.

The present study was, therefore, designed to identify clinical and functional factors related to the presence of bronchial responsiveness to inhaled propranolol in asthmatic children and adults and to ascertain the short-term repeatability of this bronchial response compared to that with methacholine. In addition, the relationship between bronchial responsiveness to propranolol and responsiveness to methacholine and to UNDW was examined.

Methods

Population

The study group consisted of 30 children (aged 7–14 yrs) and 43 adult subjects (aged 15–56 yrs), who satisfied the criteria for asthma of the American Thoracic Society [22]. All subjects answered a standard respiratory questionnaire and had skin prick tests for seven common inhalant allergens. At the time of recruitment they were in a clinical remission state or under a good pharmacological control. Subjects had not reported respiratory infection in the previous 4 weeks. Baseline values of FEV_1 had to be >70% of predicted [23]. Testing was performed out of the pollen season and at least 4 weeks after any respiratory infection. Medication requirement to control symptoms was evaluated over a period of 2 months, and the patients were divided into three therapeutic groups according to the following scheme: group I received no medication (39 subjects); group II was treated with inhaled β_2-agonists, as needed (16 subjects); group III required daily treatment with an inhaled β_2-agonist plus either beclomethasone dipropionate, or disodium cromoglycate, or both (18 subjects). Informed consent was obtained from each patient and from parents of tested children. The study was approved by the Hospital's Ethics Committee.

Study design

The study consisted of two phases. In the first phase, propranolol and methacholine challenges were performed in 73 consecutive patients and a UNDW challenge was completed by 50 patients selected randomly from the whole population. In each patient, methacholine was performed first. Inhalation tests were performed on different occasions, separated by at least 3 day intervals. Testing was completed within 2 weeks. In the second phase, repeatability of propranolol and methacholine response was assessed in a group of 22 randomly selected subjects. Measurements were completed within 2 weeks and the order of the second challenge was randomized.

Inhalation procedure

All bronchial challenges were performed between 8:30 and 10:30 a.m. Inhalation challenges with propranolol and methacholine were performed according to a standardized procedure [24], as described previously [17]. Solutions of dl-propranolol hydrochloride and methacholine chloride were freshly made every week from powder preparations (Sigma, Chemical Co., USA). Before testing, double increasing concentrations (from 0.03–32 $mg \cdot ml^{-1}$) were prepared by dilution in phosphate buffered-saline. Aerosols of each solution were generated by a De Vilbiss 646 nebulizer connected to a French-Rosenthal dosimeter. This system delivered an average of 9.1 µl of solution when activated for 0.6 s. Initially, we administered five breaths of control buffered solution, followed by the inhalation of doubling increasing concentrations of each drug. Forced expiratory flow-volume curves were recorded before and after the control buffered solution, and 0.5, 1.5, and 3 min after each inhalation. The procedure was discontinued when the FEV_1 dropped by 20% or more from the lowest value recorded after control solution, or until a maximum dose of propranolol (100 µmol) and methacholine (30 µmol) was reached. The cumulative dose-response curve was constructed by plotting the logarithmic value of the dose against the percentage decrease in FEV_1 value. The provocative dose producing a 20% fall in FEV_1 ($PD_{20}FEV_1$) was then calculated by linear interpolation of the two last points, and expressed in µmol.

Inhalation challenge with UNDW was performed following a standard protocol, as described previously [25]. In brief, the aerosols were generated by a Mistogen EN 145 ultrasonic nebulizer, which was calibrated to produce five increasing outputs. The outputs of UNDW used were 0.5, 1.0, 1.8, 3.6 and 5.6 $ml \cdot min^{-1}$. Subjects were connected to a face-mask with clipped nose and required to breathe tidally for 3 min at each output. Volume outputs were delivered at 5 min intervals. Forced expiratory flow-volume curves were recorded before and 0.5, 1.5, and 3 min after each inhalation. The procedure was discontinued when the FEV_1 dropped by 20% or more from the lowest baseline FEV_1 value, or the maximum volume output was administered. The stimulus-response curve was constructed by plotting the volume output of the nebulizer, as logarithmic value against the percentage decrease in FEV_1 from the lowest baseline FEV_1 value. Bronchial responsiveness to UNDW was calculated by linear interpolation of the last two experimental points and expressed as provocative output of UNDW producing a 20% fall in FEV_1 (PO_{20}UNDW) ($ml \cdot min^{-1}$). Patients were defined as responders when a PO_{20}UNDW was measurable, and nonresponders when FEV_1 fell less than 20% after the highest UNDW output.

Statistical analysis

PD_{20} values were logarithmically transformed before analysis. Determinants of bronchial responsiveness to propranolol were examined by multiple step-forward

regression analysis by taking $PD_{20}P$ values as dependent variables and age, gender, age at asthma onset, presence of atopy, baseline FEV_1 and $PD_{20}M$ values as independent variables. Gender and atopy were used as dummy variables. Normality of distribution of either $PD_{20}P$ and $PD_{20}M$ values was tested by Kolmogorov-Smirnov's test. Comparison of bronchial sensitivity to inhaled propranolol and methacholine, expressed as PD_{20} values, was performed according to the method proposed by BLAND and ALTMAN [26]. Differences in $PD_{20}P$ and $PD_{20}M$ between treatment groups were examined by one-way analysis of variance (ANOVA) and Student-Newman-Keul's test [27]. Differences in $PD_{20}P$ and $PD_{20}M$ between responders and non-responders to UNDW were examined by one-way ANOVA [27]. Reproducibility of responses was assessed by calculating the coefficient of repeatability [26], and the intraclass correlation coefficient, derived from a two-way ANOVA [27]. A p-value of ≤ 0.05 was considered significant.

Table 1. – Anthropometric clinical and functional data of each asthmatic patient included in first therapeutic group

						Propranolol Ch.		Methacholine Ch.		UNDW Ch.*	
Pt no.	Age yrs	Sex	Atopy	Age at asthma onset yrs	FEV_1 pred. *l*	FEV_1 % pred	$PD_{20}FEV_1$ µmol	FEV_1 % pred	$PD_{20}FEV_1$ µmol	FEV_1 % pred	$PO_{20}FEV_1$ ml·min^{-1}
1	14	M	Y	2	3.19	90	4.54	98	0.23	94	1.72
2	9	M	Y	7	1.54	116.	7.45	116	1.27	115	>5.2
3	14	M	Y	12	3.65	93	4.58	101	0.19	94	>5.2
4	11	M	Y	9	2.60	92	29.77	89	0.17	97	4.21
5	13	M	N	12	2.82	102	35.31	95	0.09	98	>5.2
6	14	M	Y	4	3.05	93	15.17	92	0.67	88	>5.2
7	9	M	Y	5	1.86	99	10.17	108	0.10	108	>5.2
8	12	M	Y	11	3.01	89	22.55	96	7.99	98	>5.2
9	18	M	Y	12	4.11	97	0.14	93	0.12	90	0.63
10	14	M	N	12	3.74	94	13.32	97	11.19	96	>5.2
11	16	F	Y	12	3.43	99	3.83	104	0.19	101	1.84
12	12	F	N	3	2.29	102	0.02	102	0.19	98	0.77
13	12	M	Y	6	2.18	91	4.22	86	0.17	90	1.43
14	14	F	Y	3.5	2.83	105	2.92	106	0.05	113	>5.2
15	8	M	Y	1.5	1.54	92	1.09	92	0.36	97	0.91
16	11	F	Y	5	2.30	105	16.43	106	1.22	107	>5.2
17	11	F	Y	0.5	2.17	105	8.95	10	0.66	103	4.76
18	11	M	Y	6	2.50	92	3.73	90	0.10	90	>5.2
19	9	M	Y	3	1.95	104	8.49	101	0.23	95	>5.2
20	13	M	Y	6	3.38	113	51.20	112	10.08	112	>5.2
21	11	M	N	0.5	2.60	97	29.20	97	7.59	97	>5.2
22	23	M	Y	18	4.15	100	>100	97	2.49	ND	ND
23	43	F	N	40	2.81	101	>100	108	3.05	ND	ND
24	17	M	N	3.5	4.16	86	9.07	94	1.15	ND	ND
25	27	M	Y	20	4.11	117	31.16	119	0.94	ND	ND
26	21	M	N	3	4.11	89	7.61	90	0.54	ND	ND
27	30	F	Y	16	3.00	102	8.40	104	1.93	ND	ND
28	37	F	N	36	2.72	98	6.09	103	0.28	99.5	2.56
29	52	F	N	17	2.54	104	11.21	110	0.52	ND	ND
30	15	F	Y	12	3.02	142	89.91	149	4.06	ND	ND
31	47	M	N	46	3.57	83	36.50	78	3.46	ND	ND
32	21	M	Y	3	3.97	75	28.51	74	10.75	ND	ND
33	30	F	N	28	2.60	127	8.02	122	2.05	119	>5.2
34	17	M	Y	15	4.69	109	12.90	113	3.37	106	>5.2
35	17	M	N	17	4.16	102	3.76	103	0.10	92	>5.2
36	22	M	Y	1	4.46	98	1.55	102	0.27	87	1.15
37	17	M	Y	12	4.00	103	6.76	100	0.02	103	2.49
38	20	M	Y	4	4.51	125	41.11	124	3.67	113	>5.2
39	49	M	N	48	3.31	86	>100	91	0.13	80	>5.2
Mean	21			12.1	3.14	100.4		102		99	
±SD	11.6			12.2	0.86	12.7		13.2		9.4	
GM							7.69		0.64		1.68

FEV_1: forced expiratory volume in one second; PD_{20}: provocative dose causing a 20% fall in FEV_1: UNDW: ultrasonically nebulized distilled water; PO_{20}: provocative output causing a 20% fall in FEV_1; Pt: patient; Ch: challenge; *: when PO_{20} was not determined, >5.2 was reported; ND: not done; GM: geometric mean.

Results

The clinical and functional data of the asthmatic population, grouped according to their treatment requirements are reported in tables 1–3. Mean values (±SD) of baseline FEV_1 as percentage of predicted, measured on propranolol and methacholine days were not statistically different (99.5±14.7 and 100.6±14.6, respectively). Individual values of $PD_{20}P$ and $PD_{20}M$ are illustrated in figure 1. Three patients did not respond up to 100 μmol of inhaled propranolol, whereas all subjects responded to methacholine. The geometric means (±GSEM) for $PD_{20}P$ and $PD_{20}M$ were 6.07±1.21 μmol (range 0.012–89.9 μmol) and 0.44±1.19 μmol (range 0.02–11.6 μmol), respectively.

Table 2. – Anthropometric clinical and functional data of each asthmatic patient included in second therapeutic group

				Age at asthma	FEV_1	Propranolol Ch.		Methacholine Ch.		UNDW Ch.*	
Pt no.	Age yrs	Sex	Atopy	onset yrs	pred. *l*	FEV_1 % pred	$PD_{20}FEV_1$ μmol	FEV_1 % pred	$PD_{20}FEV_1$ μmol	FEV_1 % pred	$PO_{20}FEV_1$ ml·min^{-1}
1	13	M	Y	1	2.92	81	3.71	86	0.08	88	3.01
2	9	M	Y	1.5	1.59	97	3.12	106	0.29	104	2.06
3	9	M	Y	6	1.68	97	14.75	97	0.30	101	>5.2
4	10	M	Y	9	2.69	96	8.97	93	0.32	95	>5.2
5	10	M	Y	0.5	2.18	84	9.22	89	1.72	88	>5.2
6	15	F	Y	5	2.97	131	6.34	125	0.76	129	3.57
7	20	F	Y	14	3.42	74	5.88	82	0.78	82	>5.2
8	16	M	Y	2	3.93	110	11.81	117	1.38	ND	ND
9	23	M	N	14	4.29	114	14.88	108	0.55	ND	ND
10	19	M	N	1.5	3.74	83	10.24	91	0.39	ND	ND
11	34	F	Y	3	2.76	99	3.14	102	0.16	ND	ND
12	27	M	Y	20	3.9	124	14.35	121	0.19	ND	ND
13	35	M	Y	34	4.21	101	4.79	98	0.43	ND	ND
14	35	M	N	22	3.84	79	2.27	84	2.35	ND	ND
15	11	F	Y	3	1.95	86	3.90	86	0.02	86	>5.2
16	7	M	Y	5	1.82	96	15.10	103	1.44	93	>5.2
Mean	18			9	2.99	97		99		96	
±SD	9.8			9.6	0.94	16.3		13.5		14.1	
GM							6.91		0.41		2.81

*: when PO_{20} was not determined, >5.2 was reported. For abbreviations see legend to table 1.

Table 3. – Anthropometric clinical and functional data of each asthmatic patient included in third therapeutic group

				Age at asthma	FEV_1	Propranolol Ch.		Methacholine Ch.		UNDW Ch.*	
Pt no.	Age yrs	Sex	Atopy	onset yrs	pred. *l*	FEV_1 % pred	$PD_{20}FEV_1$ μmol	FEV_1 % pred	$PD_{20}FEV_1$ μmol	FEV_1 % pred	$PO_{20}FEV_1$ ml·min^{-1}
1	13	M	Y	3	2.59	94	4.78	92	0.10	89	1.03
2	16	F	N	14	3.05	95	7.38	98	0.24	92	0.67
3	15	F	Y	7	2.70	116	8.69	112	0.38	118	>5.2
4	10	M	Y	5	2.18	90	4.81	86	0.15	85	>5.2
5	14	M	Y	3	4.25	108	2.74	111	0.05	109	1.37
6	12	M	Y	0.5	2.27	85	0.01	83	0.02	85	1.11
7	41	F	N	37	2.66	99	10.23	103	1.14	ND	ND
8	17	M	N	2	3.23	103	11.10	98	0.06	ND	ND
9	28	M	Y	20	4.08	86	3.62	86	0.85	ND	ND
10	56	F	N	7	2.54	72	22.03	71	1.57	ND	ND
11	23	M	Y	20	4.55	134	9.65	137	0.42	132	>5.2
12	25	M	Y	12	5.10	85	9.69	89	0.58	82	3.12
13	41	F	Y	40	2.61	135	0.04	136	0.06	121	0.58
14	25	M	Y	20	4.11	96	1.01	95	0.23	91	3.24
15	18	M	Y	4	4.19	93	2.03	85	0.12	ND	ND
16	16	M	Y	10	4.35	102	6.79	110	0.37	97	>5.2
17	27	M	Y	26	4.99	80	24.67	81	1.04	76	>5.2
18	21	M	Y	1.5	4.47	124	4.74	124	0.04	ND	ND
Mean	23			13	3.55	100		100		98	
±SD	12.1			12.0	0.99	18		18.7		17.8	
GM							3.36		0.21		1.29

*: when PO_{20} was not determined, >5.2 was reported. For abbreviations see legend to table 1.

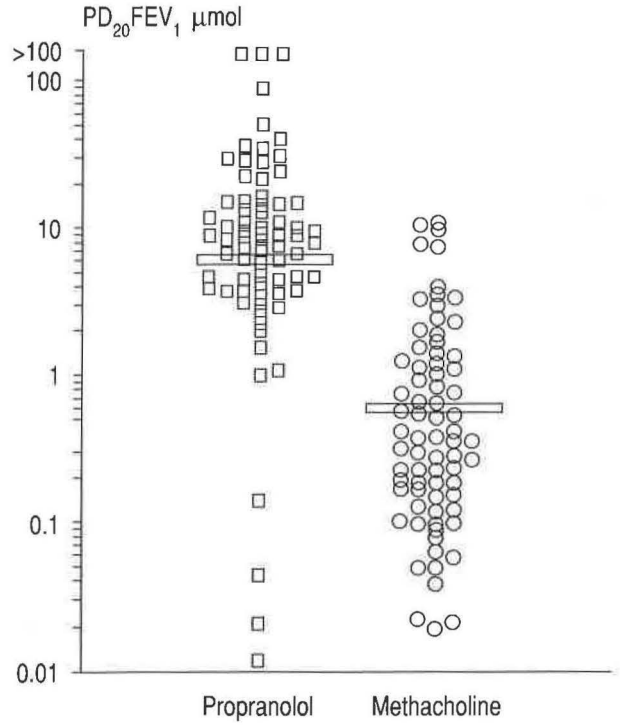

Fig. 1. – Individual values of $PD_{20}FEV_1$ for propranolol and methacholine (µmol) in the whole asthmatic population. Bars represent geometric mean values. $PD_{20}FEV_1$: provocative dose producing a 20% fall in expiratory volume in one second; □: propranolol; ○: methacholine.

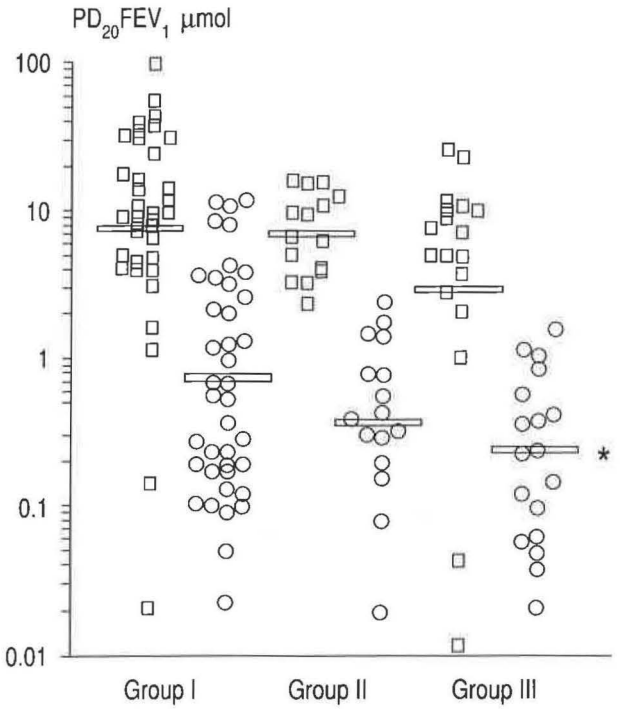

Fig. 2. – Individual values of $PD_{20}FEV_1$ for propranolol and methacholine (µmol) in 70 asthmatic subjects, grouped according to their treatment requirement. Bars represent geometric mean values. *: $p<0.05$ ($PD_{20}M$ in Group III compared to Group I). □: propranolol; ○: methacholine (M). For abbreviations see legend to figure 1.

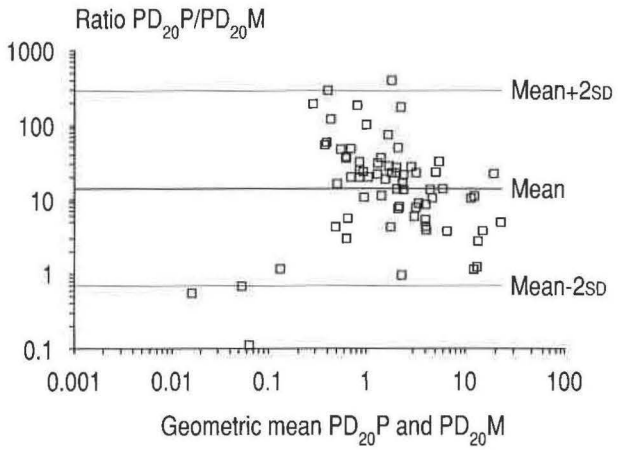

Fig. 3. – Relationship in each asthmatic subject (n=70) between geometric mean of $PD_{20}P$(µmol) and $PD_{20}M$ (µmol) and the difference between $PD_{20}P$ and $PD_{20}M$. For abbreviations see legend to figure 1.

Propranolol responsiveness was not related to age, gender, age at asthma onset, presence of atopy, and baseline FEV_1 as percentage of predicted value, whereas it was significantly related to the degree of methacholine responsiveness (by multiple step-forward regression analysis, $p<0.001$).

There was no significant difference as regards age, length of asthmatic history and baseline FEV_1 among therapeutic groups (fig. 2). Mean $PD_{20}P$ values were not significantly different between each group, whilst mean $PD_{20}M$ value of Group III was significantly lower compared to value of Group I ($p<0.05$). There was a large overlap of $PD_{20}P$ and $PD_{20}M$ among groups (fig. 2).

The ratio of $PD_{20}P$ and $PD_{20}M$ and the geometric mean PD_{20} of the two determinations in 70 asthmatic patients is illustrated in figure 3. The ratio of geometric mean $PD_{20}P$ to geometric mean $PD_{20}M$ was 14.1 (95% confidence limit (95% CL) 9.9–20.2). The limits of agreement between pairs of PD_{20} were -0.37 to 5.66.

Repeatability of $PD_{20}P$ and $PD_{20}M$ was examined in a group of 22 subjects (6 females; aged 9–56 yrs). Mean values of baseline FEV_1, as percentage of predicted, measured on the four days of study were not statistically different (propranolol days: 96.8%±13.4 and 97.8%±12.9; methacholine days: 98.1%±14.1 and 97.7%±13.4). The ratio between first PD_{20} to second PD_{20} was plotted against the geometric mean of pairs of PD_{20} of either agonist, on a logarithmic scale (fig. 4). For propranolol, the ratio was 1.17 (95% CL 0.96–1.44). The coefficient of repeatability was equal to 0.94, and the intraclass correlation coefficient was 0.97. The 95% CLs for a second measurement of an additional pair of $PD_{20}P$ were 0.38 and 2.57. For methacholine, the ratio was 1.09 (95% CL 0.86–1.39). The coefficient of repeatability was equal to 1.07, and the intraclass correlation coefficient was 0.93. The 95% CLs for a second measurement of an additional pair of $PD_{20}M$ were 0.34 and 2.94.

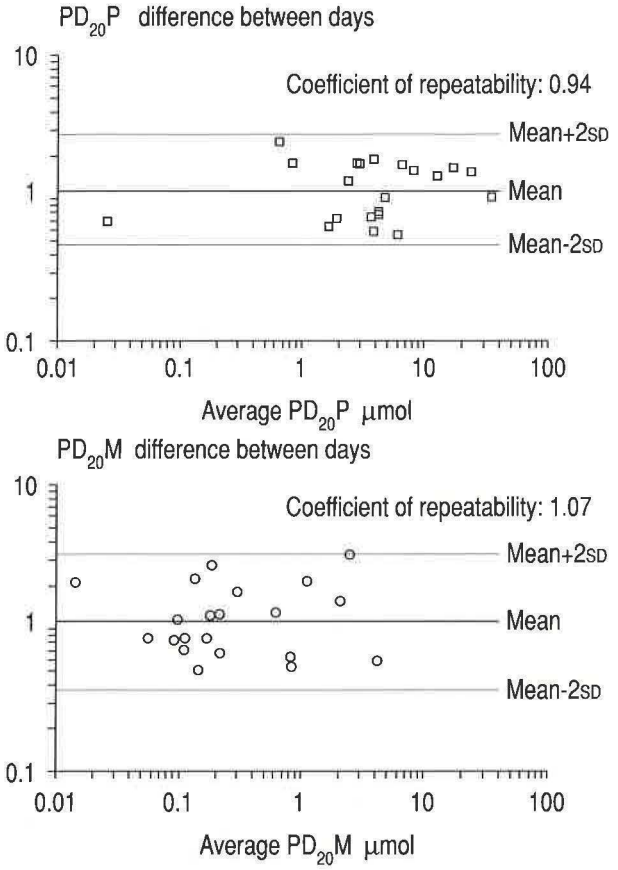

Fig. 4. – Repeatability of PD_{20} propranolol (P) (µmol) (upper panel) and PD_{20} methacholine (M) (µmol) (lower panel). For abbreviations see legend to figure 1.

Twenty one (42%) of the 50 asthmatic subjects, who performed a UNDW challenge had a measurable $PO_{20}FEV_1$ (responders). Mean values of baseline FEV_1 (±SD), as percentage of predicted, measured on the three days of study were not statistically different (99.6%±13.7, 100.7%±12.9 and 98.5%±12.5). Mean values of baseline FEV_1 (±SD), as percentage of predicted, in the UNDW responders and in the UNDW nonresponders, were not different (97.6%±11.6 and 99.2%±13.3, respectively). PO_{20}UNDW ranged between 0.58–4.76 $ml \cdot min^{-1}$. The geometric mean (±GSEM) $PD_{20}P$ in the UNDW responders was significantly lower compared to UNDW nonresponders (1.76±1.57 µmol and 11.50±1.17 µmol, respectively; $p<0.001$;). Similarly, geometric mean (±GSEM) $PD_{20}M$ in the UNDW responders was significantly lower compared to UNDW nonresponders (0.17±1.23 µmol and 0.58±1.35 µmol, respectively; $p<0.01$). In the group of 21 subjects who responded to UNDW, PO_{20}UNDW was correlated to $PD_{20}P$ (Pearson correlation coefficent=0.64, $p<0.01$), but not with $PD_{20}M$ (Pearson correlation coefficient=0.34, $p>0.1$).

Discussion

The results of this study show that inhaled propranolol causes bronchoconstriction in nearly all children and adults with asthma and that the response is reproducible. The degree of bronchial responsiveness to propranolol is related to that of methacholine, and UNDW. In addition, we have demonstrated that bronchial sensitivity to propranolol is several times lower compared to methacholine. The degree of propranolol responsiveness poorly reflected treatment requirement to control symptoms.

It has been suggested that the prevalence of a significant bronchial response to propranolol in asthmatic patients could be considerably different from methacholine and histamine [16, 28]. More recently, GERRITSEN *et al.* [19] reported that bronchial responsiveness to inhaled propranolol was measurable in only two-thirds of a group of asthmatic children, whereas OKAYAMA *et al.* [18] found a significant response in all adult asthmatics tested. Our study demonstrates that $PD_{20}P$ is measurable in more than 95% of patients with asthma and that there is no age difference in terms of responsiveness to propranolol. In addition to selection of patients, discrepancies are likely to be due to the different pulmonary parameters used to ascertain the bronchial response and to the maximal delivered dose of propranolol. Our results confirm that inhaled propranolol is a far less potent bronchoconstrictive agent compared to methacholine [17] or histamine [29]. The analysis of agreement proposed by BLAND and ALTMAN [26] allowed us to assess this difference. In the overall population, the ratio between geometric mean $PD_{20}P$ and $PD_{20}M$ is 14.1. Very few asthmatic subjects had $PD_{20}P$ lower than $PD_{20}M$. This indicates that the mechanisms of action of the two drugs could be rather different. In addition, we found that $PD_{20}P$ and $PD_{20}M$ are equally well reproducible. The confidence limits for repeated PD_{20} measurements suggested that a 2.5 fold increase in $PD_{20}P$ and a three fold increase in $PD_{20}M$ are statistically significant. Repeatability of $PD_{20}M$ in our population was comparable, although slightly lower than that reported by others [24, 30, 31]. Overall, bronchial responsiveness to either propranolol or methacholine poorly reflects treatment requirement. The relationship between treatment requirement and bronchial responsiveness to either methacholine or histamine in asthma has been examined in several studies [32–35], whereas the relationship to propranolol responsiveness has never previously been investigated. Our results confirm that a single measurement of responsiveness to methacholine inadequately reflects the clinical state of the disease for a given asthmatic patient [35], and suggest that $PD_{20}P$ is also a poor predictor of asthma severity.

The mechanism of bronchoconstriction induced by propranolol is probably rather complex. Although, it is still not completely clear [36], it probably acts as an indirect stimulus [20] through a vagal pathway. This hypothesis is supported by the protective effect of anticholinergic drugs [37–39]. However, it probably involves other pathways, since the protective effect of anticholinergic drugs is enhanced by inhaled vasoactive intestinal peptide, which also possess a protective effect when given alone [39]. Interestingly,

at variance with methacholine responsiveness, propranolol responsiveness is not modified by treatment with inhaled steroids [40].

Although, propranolol responsiveness appears to reflect the presence of bronchial responsiveness and can be safely measured in either children or adults with asthma, it does not appear to have any particular advantage on other more conventional stimuli. However, it is worth mentioning that the assessment of propranolol responsiveness has been shown to provide a better separation between asthmatics and patients with chronic obstructive pulmonary disease when compared to histamine [41].

In conclusion, the results of this study confirm and extend previous works by demonstrating a significant and reproducible bronchial response to propranolol in nearly all children and adults with asthma. It seems that there is a constant difference in sensitivity of bronchial airways to inhaled propranolol as compared to methacholine in asthma. Bronchial challenge can be reliably performed in asthmatic patients and appears to be an interesting tool for research purposes. Finally, it would be worth determining factors leading to a significant bronchial response with a very low dose of inhaled propranolol as well as understanding reasons for the absence of response in some asthmatic patients.

Acknowledgements: The authors wish to thank L. Marazzini for reviewing the manuscript.

References

1. McNeil RS. – Effect of a beta-adrenergic blocking agent, propranolol, on asthmatics. *Lancet* 1964; ii: 1101–1102.
2. Zaid G, Beall GM. – Bronchial response to beta-adrenergic blockade. *N Engl J Med* 1966; 275: 580–584.
3. McNeil RS, Ingram CG. – Effect of propranolol on ventilatory function. *Am J Med* 1966; 18: 473–475.
4. MacDonald AG, Ingram CG, McNeil RS. – The effect of propranolol aerosol in asthmatic subjects. *J Physiol* 1967; 190: 41P.
5. Langer IM. – The bronchoconstrictor action of propranolol aerosol in asthmatic subjects. *J Physiol* 1967; 190: 41P.
6. Beumer HM. – Inhalation of beta-adrenergic blockers by asthmatics. *Lancet* 1967; ii: 993.
7. MacDonald AG, McNeil RS. – A comparison of the effect on airway resistance of a new beta-blocking drug, ICI.50, 172 and propranolol. *J Anaesth* 1968; 40: 508–510.
8. Beumer HM. – Local effects of beta-adrenergic blocking drugs in histamine sensitive asthmatics. *Pharm Clinica* 1969; 1: 172–173.
9. Richardson PS, Sterling GM. – Effect of β-adrenergic receptor blockade on airway conductance and lung volume in normal and asthmatic subjects. *Br Med J* 1969; 3: 143–145.
10. Beumer HM, Hardonk HJ. – Effect of beta-adrenergic blocking drugs on ventilatory function in asthmatics. *Eur J Clin Pharmacol* 1972; 5: 77–80.
11. Gayrard P, Orehek J, Grimaud C, Charpin J. – Beta-adrenergic function in airways of healthy and asthmatic subjects. *Thorax* 1975; 30: 657–662.
12. Dunn TL, Gerber MJ, Shen AS, *et al.* – The effect of topical ophthalmic instillation of timolol and betaxolol on lung function in asthmatic subjects. *Am Rev Respir Dis* 1986; 133: 264–268.
13. Beumer HM. – Adverse effects of β-adrenergic receptor blocking drugs on respiratory function. *Drugs* 1974; 7: 130–138.
14. Tattersfield AE, Harrison RN. – Effect of beta-blocker therapy on airway function. *Drugs* 1983; 25 (Suppl. 2): 227–231.
15. Gayrard P, Orehek J, Charpin J. – Le test au propranolol: nouveau test de provocation de l'asthme. *Rev Tuberc Pneumol* 1971; 35: 511–522.
16. De Vries K, Köeter GH, Gökemeyer JDM. – Some aspects of the regulation of the bronchial tree in obstructive lung disease. *Eur J Respir Dis* 1982; 63 (Suppl. 121): 60–63.
17. Foresi A, Chetta A, Corbo GM, Cuomo A, Olivieri D. – Provocative dose and dose-response curve to inhaled propranolol in asthmatic subjects with hyperresponsiveness to methacholine. *Chest* 1987; 92: 455–459.
18. Okayama M, Yafuso N, Nogami H, *et al.* – A new method of inhalation challenge with propranolol: comparison with methacholine-induced bronchoconstriction and role of vagal nerve activity. *J Allergy Clin Immunol* 1987; 80: 291–299.
19. Gerritsen J, Köeter GH, Van Der Weele LT, Knol K. – Propranolol inhalation challenge in relation to histamine response in children with asthma. *Thorax* 1988; 43: 451–455.
20. Pauwels R, Joos G, Van Der Straten M. – Bronchial hyperresponsiveness is not bronchial hyperresponsiveness is not bronchial asthma. *Clin Allergy* 1988; 18: 317–321.
21. Chetta A, Foresi A, Garavaldi G, *et al.* – Evaluation of bronchial responsiveness by pharmacological challenges in asthma. Inhaled propranolol in comparison with histamine and methacholine. *Respiration* 1988; 54 (Suppl. 1): 84–89.
22. American Thoracic Society. – Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. *Am Rev Respir Dis* 1987; 136: 225–244.
23. Knudson RJ, Slatin RC, Lebowitz MD, Burrows B. – The maximal expiratory flow-volume curve: normal standards, variability and effect of age. *Am Rev Respir Dis* 1976; 113: 587–600.
24. Ryan G, Dolovich MB, Roberts RS, *et al.* – Standardization of inhalation provocation tests: two techniques of aerosol generation and inhalation compared. *Am Rev Respir Dis* 1981; 123: 195–199.
25. Foresi A, Mattoli S, Corbo GM, Polidori G, Ciappi G. – Comparison of bronchial response to ultrasonically nebulized distilled water, exercise and methacholine in asthma. *Chest* 1986; 90: 822–826.
26. Bland JM, Altman DG. – Statistical methods for assessing agreement between two methods for clinical measurements. *Lancet* 1986; i: 307–310.
27. Winer BJ. – Statistical principles in experimental design. 2nd ed, New York, McGraw-Hill Book Co., 1971.
28. De Vries K, Gökemeyer JDM, Köeter GH, et *al.* – Cholinergic and adrenergic mechanisms in bronchial hyperreactivity. *In*: Morley J, ed. Bronchial hyperreactivity. London, Academic Press, 1982; pp. 107–121.
29. Woolcock AJ, Cheung W, Salome C. – Relationship between bronchial responsiveness to propranolol and histamine. *Am Rev Respir Dis* 1984; 129: A177.
30. Juniper EF, Frith PA, Dennett C, Cockroft DW,

Hargreave FE. – Reproducibility and comparison of responses to inhaled histamine and methacholine. *Thorax* 1978; 33: 705–710.
31. Connoly MJ, Avery AJ, Walters EH, Hendrick DJ. – The relationship between bronchial responsiveness to methacholine and bronchial responsiveness to histamine in asthmatic subjects. *Pulm Pharmacol* 1988; 1: 53–58.
32. Cockroft DW, Killian DN, Mellon JJA, Hargreave FE. – Bronchial reactivity to inhaled histamine: a method and clinical survey. *Clin Allergy* 1977; 7: 235–243.
33. Murray AB, Ferguson AC, Morrison B. – Airway responsiveness to histamine as a test for overall severity of asthma in children. *J Allergy Clin Immunol* 1981; 68: 119–124.
34. Juniper EF, Frith PA, Hargreave FE. – Airway responsiveness to histamine and methacholine: relationship to minimum treatment to control symptoms of asthma. *Thorax* 1981; 36: 575–579.
35. Josephs LK, Gregg I, Mullee MA, Holgate ST. – Nonspecific bronchial reactivity and its relationship to the clinical expression of asthma. A longitudinal study. *Am Rev Respir Dis* 1989; 140: 350–357.
36. Barnes PJ. – Muscarinic receptors subtypes: implication for lung disease. *Thorax* 1989; 44: 161–167.
37. Köeter GH, Meuers H, Jonkman JHG, *et al.* – Protective effect of oral oxyphenomium bromide, terbutaline and theophylline against the bronchial obstructive effects of inhaled histamine, acetylcholine and propranolol. *Eur J Clin Pharmacol* 1984; 26: 435–441.
38. Ind PW, Dixon CMS, Fuller RW, Barnes PJ. – Anti-cholinergic blockade of beta-blocker induced bronchoconstriction. *Am Rev Respir Dis* 1989; 139: 1390–1394.
39. Crimi N, Palermo N, Olivieri R, *et al.* – Effect of vasoactive intestinal peptide (VIP) on propranolol-induced bronchoconstriction. *J Allergy Clin Immunol* 1988; 82: 617–621.
40. Kraan, J, Köeter GH, van der Mark Th, Sluiter HJ, De Vries K. – Changes in bronchial hyperreactivity induced by 4 weeks of treatment with anti-asthmatic drugs in patients with allergic asthma: a comparison between budesonide and terbutaline. *J Allergy Clin Immunol* 1985; 76: 628–636.
41. Woolcock AJ, Anderson SD, Peat JK, *et al.* – Characteristics of bronchial hyperresponsiveness in chronic obstructive pulmonary disease and in asthma. *Am Rev Respir Dis* 1991; 143: 1438–1443.