

Propranolol inhalation challenge in relation to histamine response in children with asthma

J GERRITSEN, G H KOËTER, L T VANDERWEELE, K KNOL

From the Paediatric and Internal Departments of Pulmonology, and the Computing Centre, University Hospital, Groningen, and University of Groningen, The Netherlands

ABSTRACT The relation between airway responsiveness to propranolol and histamine was studied in 32 asthmatic children. Propranolol and histamine were given by nebuliser to a maximum dose of 16 mg/ml and 32 mg/ml respectively and the response was measured as the provocative concentration of agonist causing a 20% fall in FEV₁ (PC₂₀). A PC₂₀ histamine value of less than 32 mg/ml was obtained in 24 of the 32 children, of whom 15 had a measurable PC₂₀ propranolol (< 16 mg/ml). In these 24 children the geometric mean PC₂₀ histamine was 4.5 mg/ml and 14.4 mg/ml respectively in those with and without a measurable PC₂₀ propranolol ($p = 0.023$). There was a linear relationship between histamine and propranolol PC₂₀ values ($r = 0.60$), and between PC₂₀ histamine and FEV₁ % predicted ($r = 0.43$), but not between PC₂₀ propranolol and FEV₁ % predicted ($r = 0.38$). In an open time course study in 12 children with asthma recovery of FEV₁ after inhaled propranolol was incomplete in seven of the children after 90 minutes. When inhaled propranolol was followed by inhaled ipratropium bromide in a further 11 children FEV₁ had returned to baseline in all children after 60 minutes. Thus propranolol inhalation can be used in children with asthma to assess the contribution of the β adrenergic system to the regulation of bronchial smooth muscle tone. The test has several disadvantages in comparison with histamine provocation—long duration, the prolonged action of propranolol, and the fact that only the children with substantial hyperreactivity to histamine react to propranolol.

Introduction

Soon after the introduction of the non-selective β receptor blocking agent propranolol, it was reported that administration could lead to bronchoconstriction in patients with asthma,^{1,2} whether the drug was administered orally, intravenously, or by inhalation.¹⁻⁴ The development of bronchoconstriction after propranolol has been considered by some workers to be a feature of bronchial hyperreactivity.^{5,6} Bronchial hyperreactivity is often assessed as the airway response to histamine or methacholine, agonists acting on histamine and muscarinic receptors on bronchial smooth muscle.⁷⁻¹⁰ The adrenergic system can be considered as a counter-regulating mechanism,¹¹ causing bronchodilatation and attenuating bronchial hyperreactivity.

In the present study the relation between propranolol and histamine responsiveness of the airways

was investigated in children with asthma, to assess the relation between the β adrenergic action on the airways and the degree of bronchial hyperreactivity. Children with increased airway reactivity were expected to be more likely to develop bronchoconstriction with propranolol. If they did, a clear relation between the degree of responsiveness to histamine and to propranolol was to be expected. In addition, the time course of change in FEV₁ after propranolol inhalation was determined. The influence of inhaled ipratropium bromide on this time course was documented in a parallel group of children.

Methods

PATIENTS

Fifty five asthmatic children (20 girls), aged 9-15 years, were studied after we had received informed consent from both the children and their parents. The study was approved by the institution's committee on clinical investigation. The diagnosis of asthma was based on a history of episodic shortness of breath or wheezing (or both), either permanently or episodically. All the children were judged atopic on the

Address for reprint requests: Dr Jorrit Gerritsen, Department of Paediatrics, Division of Paediatric Pulmonology, 59 Oostersingel 9713 EZ Groningen, The Netherlands.

Accepted 23 March 1988

basis of a positive skin response to at least one allergen on skin testing. Baseline FEV₁ values were not below 70% of predicted.¹² At the time of the study asthma was under control and none of the subjects was receiving oral corticosteroids or sustained release theophylline preparations. Maintenance treatment included sodium cromoglycate or low dose inhaled corticosteroids and a β_2 agonist on an "if needed" basis; this was withheld for at least 24 hours before each test.

In 32 children propranolol and histamine challenges were performed. In 23 children known to develop bronchoconstriction in response to propranolol the time course of the FEV₁ change was determined after inhalation of propranolol alone (12 children) or after inhalation of propranolol followed by ipratropium bromide.

HISTAMINE CHALLENGE

Aerosols of test solutions were generated by passing air through a gauged Wiesbadener Doppelinhaler at a flow rate of 8 l/min as described previously.¹³ This results in an aerosolised volume of 110–120 μ l/min and a droplet size of less than 5 μ m.¹⁴ Aerosols were inhaled by tidal breathing for 30 seconds. The children wore a nose clip during inhalation and lung function manoeuvres. After having baseline spirometry the children inhaled a control solution of saline 9 g/l, followed at three minute intervals by doubling concentrations of histamine acid phosphate, starting at 0.25 mg/ml and going up to a maximum of 32 mg/ml. A water seal spirometer (Spirograph, Lode spirometer D75, Groningen, The Netherlands) was used for measurements of the inspiratory slow vital capacity (VC) and FEV₁. The FEV₁ was measured immediately, and again three minutes after each inhalation. Inhalations were discontinued when the FEV₁ had fallen by 20% from baseline FEV₁ or after the 32 mg/ml concentration of histamine had been administered.

PROPRANOLOL CHALLENGE

Propranolol inhalation tests were carried out at least 60 minutes after the histamine challenge test and when the FEV₁ had returned to within 95% of baseline. Propranolol solutions were nebulised in the same way as histamine, and inhaled for two minutes in accordance with the propranolol provocation scheme in adults.^{5,11} The challenge was performed with the following concentrations of propranolol in saline 9 g/l: 1.0, 2.0, 4.0, 8.0, and 16.0 mg/ml. The solutions had a pH of 6.60, 6.42, 6.30, 6.20, and 5.98 respectively. Inhalations were stopped when the FEV₁ had fallen by 20% from the baseline value, or after the maximum concentration had been administered.

TIME COURSE OF CHANGE IN FEV₁ AFTER PROPRANOLOL INHALATION

The time course of change in FEV₁ after challenge with

propranolol was measured in an open study in parallel groups of 12 and 11 children, selected on the basis of having a bronchoconstrictor response to inhaled propranolol. In the first group change in FEV₁ after inhaled propranolol was followed for up to 90 minutes. In the second group ipratropium bromide 0.25 mg/ml was inhaled for two minutes (Wiesbadener doppeinhaler) 15 minutes after the propranolol challenge, and change in FEV₁ was followed for further 45 minutes.

ANALYSIS OF RESULTS

Response to histamine and propranolol was expressed as the provocation concentration of agonist required to cause a 20% fall in FEV₁ (PC₂₀). This was obtained by fitting a "smoothed" curve to the last three points on the dose-response curve with the help of a Cyber computer, the concentration being measured at 80% of the pretest FEV₁.¹⁵ Logarithmic transformation were applied to all PC₂₀ values before analysis. PC₂₀ values (mg/ml) are presented as geometric means, and FEV₁ values as means with standard errors. The relationship between PC₂₀ propranolol and PC₂₀ histamine values and baseline FEV₁ (as percentages of predicted values) was assessed by means of Pearson correlation coefficient. Student's *t* test for unpaired observations was used to compare the FEV₁ predicted values of children with a PC₂₀ propranolol of 16 mg/ml or less and of those with a value of more than 16 mg/ml. Statistical analysis of the data was performed with the SPSS-X program (Statistical Package for the Social Sciences, version X) on the University Cyber 170/760 computer.

Results

Details of the children are given in tables 1 and 2. After inhalation of the maximum concentration of propranolol (16 mg/ml) a few children complained of local irritation of the mouth and an unpleasant taste. The mean FEV₁ was 92.8 (1.1) % predicted for all the children, ranging from 73% to 108%. A PC₂₀ histamine was obtained in 24 of the 32 children challenged with both histamine and propranolol. Of these 24 children, 15 had a measurable PC₂₀ propranolol and nine did not. All of the 14 children with PC₂₀ histamine of value of more than 16 mg/ml had a PC₂₀ propranolol of more than 16 mg/ml.

PC₂₀ PROPRANOLOL VERSUS PC₂₀ HISTAMINE

There was a linear relationship between PC₂₀ histamine and PC₂₀ propranolol in the 15 children with measurable PC₂₀ value with both agonists ($r = 0.66$, $P = 0.018$; fig 1). The geometric mean PC₂₀ histamine in the 15 children with a PC₂₀ propranolol of 16 mg/ml or less was 4.5 mg/ml, compared with a mean PC₂₀

Table 1 Characteristics of 32 children receiving histamine and propranolol challenges

Age (y)	Sex	Medication*	FEV ₁ (% pred)	PC ₂₀ histamine (mg/ml)	PC ₂₀ propranolol (mg/ml)
13	F	C, β	83	1.1	1.2
11	F	C, β	81	1.8	2.5
11	M	S	88	7.6	4.5
10	M	S	90	3.5	6.6
9	M	C, β	82	1.8	6.9
12	M	S	90	3.9	8.0
11	F	C	83	3.2	9.5
10	F	S	94	2.2	10.6
9	M	No	105	14.2	11.0
10	M	S	103	14.6	11.4
10	M	C	88	5.8	11.7
14	M	C, β	73	14.4	12.3
13	F	S	99	10.6	13.1
11	F	C	100	2.8	13.5
14	M	S, β	83	4.2	13.6
12	F	C	97	4.0	> 16.0
10	M	S	95	24.0	> 16.0
15	F	S, β	92	23.8	> 16.0
11	M	No	94	18.0	> 16.0
12	M	C, β	90	4.0	> 16.0
12	M	S	94	10.0	> 16.0
13	M	S	99	26.6	> 16.0
13	M	C, β	87	19.3	> 16.0
14	F	S	100	27.2	> 16.0
10	M	S	99	> 32.0	> 16.0
9	M	No	104	> 32.0	> 16.0
12	F	C	96	> 32.0	> 16.0
14	F	S	104	> 32.0	> 16.0
9	M	S	101	> 32.0	> 16.0
13	M	S	105	> 32.0	> 16.0
10	M	S	100	> 32.0	> 16.0
11	F	C	90	> 32.0	> 16.0

*S—sodium cromoglycate; C—inhaled corticosteroids; β—sympathomimetic.

Table 2 Characteristics of 23 children in whom the time course of FEV₁ after propranolol challenge was studied

Age (y)	Sex	Medication*	PC ₂₀ propranolol (mg/ml)	FEV ₁ baseline (1)†	FEV ₁ (% pred)
<i>Twelve children whose FEV₁ improved without ipratropium bromide</i>					
12	M	C	9.0	2.0	87
12	M	S, C	3.0	1.9	84
12	M	S	15.0	2.3	99
13	F	No	16.0	2.8	105
12	M	S, β	13.3	1.9	81
15	M	S	9.9	3.6	103
9	F	C, β	12.0	1.5	92
11	M	C, β	13.0	1.9	82
13	M	S, β	16.0	1.9	80
13	M	S	15.6	2.1	88
13	F	S	15.0	2.7	92
11	F	No	8.7	2.4	108
Mean			11.3	2.2	92
12					
<i>Eleven children whose FEV₁ improved with ipratropium bromide</i>					
10	M	S	10.4	1.5	88
12	F	S	1.3	2.3	92
12	F	C, β	14.7	2.4	84
11	M	S	12.2	2.8	93
14	F	No	16.0	2.5	85
11	M	S	13.5	2.1	100
14	F	S	6.3	2.6	99
15	M	C, β	12.2	2.6	84
10	M	S	13.2	2.1	94
11	M	No	10.0	2.2	100
12	M	S	7.8	2.1	92
Mean			9.2	2.3	92
12					

*C—inhaled corticosteroids; S—sodium cromoglycate; β—sympathomimetic.
†FEV₁ before the test.

histamine of 14.4 mg/ml ($p = 0.023$) in the nine children with a PC₂₀ propranolol of over 16 mg/ml and a measurable PC₂₀ histamine.

PC₂₀ PROPRANOLOL AND FEV₁ % PREDICTED

The mean FEV₁ % predicted for the children with a measurable PC₂₀ with both propranolol and histamine (89.5% (SEM 2.4%)) did not differ significantly from values in children with a PC₂₀ propranolol of over 16 mg/ml and a PC₂₀ histamine of 32 mg/ml or less (94.2% (SEM 1.4%)), but both groups had significantly lower values than children without a measurable PC₂₀ with either challenge (99.9% (SEM 1.8%)), p being < 0.01 and < 0.05 respectively. No relationship was found between log PC₂₀ propranolol and FEV₁ % predicted values ($r = 0.38$; $p = 0.17$). A linear relationship was, however, found between log PC₂₀ histamine and FEV₁ % predicted values in the 24 children with a PC₂₀ histamine ($r = 0.43$; $p < 0.05$).

TIME COURSE OF FEV₁ AFTER PROPRANOLOL CHALLENGE AND THE INFLUENCE OF IPRATROPIUM BROMIDE

In seven of the 12 children given propranolol alone

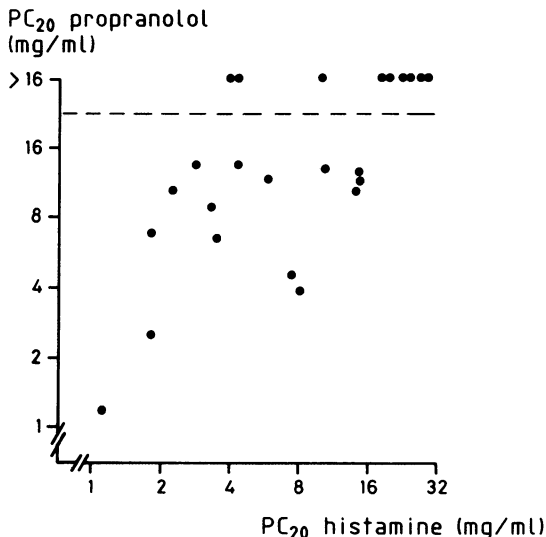


Fig 1 Provocative concentrations of histamine causing a 20% fall in FEV₁ (PC₂₀ histamine) plotted against the PC₂₀ propranolol values ($r = 0.60$; $p = 0.018$). The children who did not respond after inhalation of propranolol were assigned the value > 16 mg/ml.

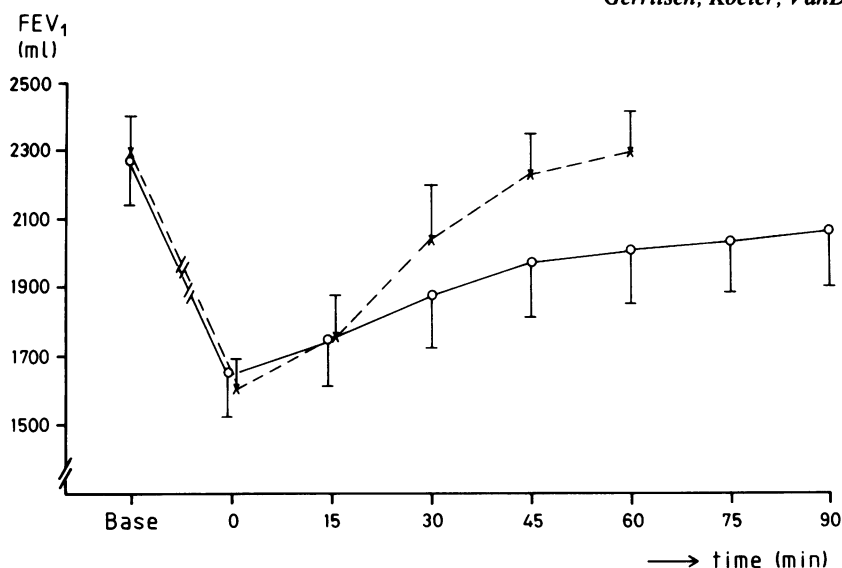


Fig 2 Mean FEV₁ before the test (base) and at threshold (0) after challenge with propranolol, and changes with time after threshold, during spontaneous recovery (○ — ○), and after treatment with ipratropium bromide 15 minutes after threshold (× — ×).

FEV₁ had not returned to within 5% of baseline values 90 minutes after challenge (fig 2). Recovery was faster in the children treated with ipratropium bromide after propranolol, FEV₁ returning to within 5% of baseline values by 60 minutes after propranolol in all 11 children (fig 2).

Discussion

In this study two thirds of the asthmatic children with a PC₂₀ histamine of less than 32 mg/ml had a bronchoconstrictor response to inhaled propranolol. A similar finding was observed in adults.⁵ PC₂₀ histamine values were significantly lower in the children who developed bronchoconstriction in response to inhaled propranolol than in the propranolol non-responders. All the children with no response to inhaled histamine also had no response to inhaled propranolol. The PC₂₀ histamine and the PC₂₀ propranolol values were clearly correlated in the children with a response to both agents. Thus an increase in non-specific reactivity is associated with an increased sympathetic drive to the airways. No correlation was observed between PC₂₀ propranolol and FEV₁ % predicted values.

The exact mechanism by which propranolol produces bronchoconstriction is not understood. It has been suggested that patients with asthma have increased cholinergic activity, and β adrenergic activity may be considered as a counter balance to oppose bronchial obstruction. Blockade of β

adrenoreceptors by propranolol will leave the cholinergic activity unopposed.¹⁶ This hypothesis is supported by the observation that in asthmatic patients prior administration of atropine can substantially reduce or even block the bronchial response to propranolol.^{16,17} There is, however, no convincing evidence suggesting how β_2 receptors are stimulated in asthmatic patients because under resting conditions circulating catecholamine concentrations are not raised.¹⁸

Other factors, such as mediator release from mast cells, may play a part in the bronchial constriction produced by propranolol. Propranolol can induce histamine release from mast cells in vitro,¹⁹ and sodium cromoglycate can inhibit the propranolol response in vivo.²⁰ No increase in circulating histamine was, however, observed after the intravenous administration of propranolol to asthmatic subjects.²¹

Only children with a PC₂₀ histamine of 16 mg/ml or less had a measurable PC₂₀ propranolol. A similar relationship has been observed previously. Subjects with the lowest PC₂₀ methacholine were most responsive to inhaled propranolol in one study,¹⁷ and the fall in FEV₁ after ocular administration of the non-selective β blocker timolol correlated with the fall in FEV₁ after an exercise challenge in another.²² Our finding of a significant correlation between airway responsiveness to histamine and to propranolol suggests that bronchial responsiveness to β adrenoreceptor blockade is substantially related to airway reactivity. The fact that prior administration of

atropine can block the response to propranolol suggests that it is predominantly determined by the degree of parasympathetic tone in the airways.

Histamine responsiveness was correlated with the degree of bronchial obstruction before challenge as in other studies.^{13,23} A similar relationship between PC₂₀ propranolol and FEV₁ % predicted values could not be found, possibly because we included only those children with an FEV₁ value of 70% or more. In adults the correlation between FEV₁ and airway reactivity is closer when FEV₁ is below 70% predicted.²⁴

The FEV₁ was slow to recover after propranolol challenge. In adults the FEV₁ was found to be over 80% of the baseline value after one hour.⁵ After 90 minutes the recovery of FEV₁ was complete in only five of the 12 children, suggesting fixed binding of propranolol to the β receptor, or delayed excretion of propranolol as a result of lipophilic properties and preferential binding to albumin.^{25,26}

Provocation with inhaled propranolol can be applied to children with asthma to assess the contribution of the β adrenergic system to the regulation of bronchial smooth muscle tone. It has, however, several disadvantages by comparison with histamine or methacholine provocation tests. These are the long duration of the test, the prolonged action of propranolol, and the fact that only the children with substantial hyperreactivity react to propranolol.

We wish to thank Leonie Logman, Obbe Norbruis, and Robert Bloem for their skilful technical assistance; Lodewijk Martijn for the illustrations; and Barbara Elliot for reviewing the text. The study was supported by the Nederlands Astma Fonds (grant 32.019).

References

- McNeill RS. Effect of a beta-adrenergic blocking agent, propranolol, on asthmatics. *Lancet* 1964;ii:1101-2.
- Zaid G, Beall GN. Bronchial response to beta-adrenergic blockade. *N Engl J Med* 1966;275:580-4.
- Wunderlich J, Macha HN, Wudicke H, Huckauf H. Beta-adrenoreceptor blockers and terbutaline in patients with chronic obstructive lung disease. Effects and interaction after oral administration. *Chest* 1980; 78:714-22.
- Beumer HM. Inhalation of beta-adrenergic blockers by asthmatics. *Lancet* 1967;ii:993.
- Gökemeyer JDM. *Hyperreactivity of the airways*. Thesis, 1976.
- Meurs H, Koëter GH, de Vries K, Kauffman HF. The beta adrenergic system and allergic bronchial asthma: changes in lymphocyte beta-adrenergic receptor number and adenylate cyclase activity after an allergen induced asthmatic attack. *J Allergy Clin Immunol* 1982;70:272-80.
- Knol K. *A clinical and epidemiological study of the significance of bronchial hyperreactivity in children with chronic specific lung disease (CNSLD)*. Thesis, 1965.
- Bhagat RG, Grunstein MM. Comparison of responsiveness to metacholine, histamine and exercise in subgroups of asthmatic children. *Am Rev Respir Dis* 1984;129:221-4.
- Hargreave FE, Dolovich J, O'Byrne PM, Ramsdale EH, Daniel EE. The origin of airway hyperresponsiveness. *J Allergy Clin Immunol* 1986;78:825-32.
- Barnes PJ. Neural control of human airways in health and disease. *Am Rev Respir Dis* 1986;134:1289-314.
- Barnes PJ. Endogenous catecholamines and asthma. *J Allergy Clin Immunol* 1986;77:791-5.
- Polgar G, Promadhat B. *Pulmonary function testing in children*. Philadelphia: WB Saunders, 1971.
- Gerritsen J, Koëter GH, Akkerboom HJ, Knol K. Recovery of FEV₁ after histamine challenge in asthmatic children. *Clin Allergy* 1987;17:119-26.
- Sterk PJ, Plomp A, Crombach MJJS, van de Vate JF, Quanjer PH. The physical properties of a jet nebulizer and their relevance for the histamine provocation test. *Bull Eur Physiopathol Respir* 1983;19:27-36.
- Eiser NM, Kerrebijn KF, Quanjer PH. Guidelines for standardization of bronchial challenges with (nonspecific) bronchoconstricting agents. *Bull Eur Physiopathol Respir* 1983;19:495-514.
- MacDonald AG, Ingram CG, McNeill RS. The effect of propranolol on airway resistance. *Br J Anaesth* 1967;39:19-26.
- Thomson NC, Daniel EE, Hargreave FE. Role of smooth muscle alpha₁-receptors in nonspecific bronchial responsiveness in asthma. *Am Rev Respir Dis* 1982;126:521-5.
- Barnes PJ, Ind PW, Brown MJ. Plasma histamine and catecholamines in stable asthmatic subjects. *Clin Sci* 1982;62:661-5.
- Terpstra GK, Raaijmakers JAK, Wassink GA. Propranolol induced bronchoconstriction: a non-specific side-effect of beta-adrenergic blocking therapy. *Eur J Pharmacol* 1981;73:107-8.
- Koëter GH, Meurs H, de Monchy JGR, de Vries K. Protective effect of disodium cromoglycate on propranolol challenge. *Allergy* 1982;37:587-90.
- Ind PW, Barnes PJ, Brown MJ, Dollery CT. Plasma histamine concentration during propranolol induced bronchoconstriction. *Thorax* 1985;40:903-9.
- Dunn TL, Gerber MJ, Shen AS, Fernandez E, Iseman MD, Cherniack RM. The effect of topical ophthalmic instillation of timolol and betaxolol on lung function in asthmatic subjects. *Am Rev Respir Dis* 1986;133:264-8.
- Juniper EF, Frith PA, Dunnett C, Cockcroft DW, Hargreave FE. Reproducibility and comparison of responses to inhaled histamine and methacholine. *Thorax* 1978;33:705-10.
- Hargreave FE, Ryan G, Thomson NC, et al. Bronchial responsiveness to histamine or metacholine in asthma: measurement and clinical significance. *J Allergy Clin Immunol* 1981;68:347-55.
- McAinsh J, Gay MA. Theoretical Michaelis-Menten elimination model for propranolol. *Eur J Drug Metab Pharmacokin* 1985;10:241-5.
- Zaagsma J, Meems L, Boorsma M. Beta-adrenoceptor studies. 4. Influence of albumin on in vitro beta-adrenoceptor blocking and antiarrhythmic properties of propranolol, pindolol, practolol and metoprolol. *Arch Pharmacol* 1977;298:29-36.