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The Safety and Effects of the Beta-Blocker, Nadolol, in Mild Asthma; An Open-label Pilot Study

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Abstract

Beta-blockers are currently contraindicated in asthma because their acute administration may be associated with worsening bronchospasm. However, their effects and safety with their chronic administration are not well evaluated. The rationale for this pilot study was based on the paradigm shift that was observed with the use of beta-blockers in congestive heart failure which once contraindicated because of their acute detrimental effects, have now been shown to reduce mortality with their chronic use. We hypothesized that certain beta-blockers may also be safe and useful in chronic asthma therapy. In this prospective, open-label, pilot study, we evaluated the safety and effects of escalating doses of the beta-blocker, nadolol, administered over 9 weeks to 10 subjects with mild asthma. Dose escalation was performed on a weekly basis based on pre-determined safety lung function, asthma control and hemodynamic parameters. The primary objective was to evaluate safety and secondary objectives were to evaluate effects on airway hyperresponsiveness, and indices of respiratory function. The escalating administration of nadolol was well tolerated. In 8 out of the 10 subjects, nine weeks of nadolol treatment produced a significant, dose-dependent increase in PC₂₀ that reached 2.1 doubling doses at 40 mg ($p < 0.0042$). However, there was also a dose-

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independent 5% reduction in mean FEV1 over the study period ($p < 0.01$). We conclude that in most patients with mild asthma, the dose-escalating administration of the beta-blocker, nadolol, is well tolerated and may have beneficial effects on airway hyperresponsiveness. Our findings warrant further testing in future larger trials.

Keywords

Asthma; beta-blockers; beta2-adrenoceptor agonist; airway hyperresponsiveness

Introduction

Asthma is a disease characterized by airway inflammation and airway hyperresponsiveness. Current pharmacological management of asthma aims at reversing bronchoconstriction, combating chronic inflammation and attenuating airway hyperresponsiveness. Beta₂-adrenoceptor (beta₂-AR) agonists are the most commonly used bronchodilators in both the acute rescue and maintenance therapy of asthma. However, chronic monotherapy with long-acting and/or short-acting beta₂-AR agonists have been associated with tolerance (1-4), an increase in airway hyperresponsiveness to allergen (5), poor asthma control (6) and even increased mortality (7); effects which may be secondary to beta₂-AR desensitization.

Non-selective beta-blockers (beta-AR antagonists or inverse agonists that block both beta₁- and beta₂-ARs) exert the exact opposite effects of beta-AR agonists and are currently contraindicated in asthma because their acute administration may produce bronchoconstriction by blocking the bronchodilating effects of endogenous adrenaline or by inactivating constitutively active beta₂-ARs. However, the effects of chronic administration of these agents in asthma have not been previously studied.

Over the last decade, a paradigm shift in the management of congestive heart failure (CHF) has occurred. Because this disease is characterized with poor cardiac muscle contractility, its treatment for decades included the use of inotropic agents such as beta-AR agonists like dobutamine, to enhance cardiac output. Paradoxically however, clinical trials in CHF showed that chronic therapy with these agents produced an increase in mortality (8,9). Concurrently, and again analogous to asthma and its management, the use of beta-blockers was once contraindicated in CHF because these drugs produce an initial negative inotropic effect and worsening of symptoms. However, pioneering studies by Waagstein and colleagues showed that chronic therapy with a beta-blocker may indeed be beneficial in the treatment of CHF (10,11). Today, certain beta-blockers are the most effective compounds available at decreasing mortality in CHF (12,13). To us, this stunning paradigm shift that occurred in CHF emphasized that *duration* of treatment was a major determinant of the observed clinical response. That is, beta-AR agonists were acutely beneficial, but chronically detrimental (9,14), and beta-blockers were acutely detrimental (15) but chronically beneficial (12,13,16-18).

Because of the analogies in asthma and heart failure with regard to the use and contraindication of beta-AR agonists and antagonists, and the results of the CHF experience, we examined the effect of chronic administration of beta-blockers in asthma. We first observed that in a murine model of antigen-induced airway inflammation and hyperresponsiveness, *duration* of therapy was, exactly as in CHF, the determinant of response to beta-AR ligands (19). That is, acute treatment with certain beta-blockers increased airway hyperresponsiveness, while chronic treatment (28 days) significantly decreased airway hyperresponsiveness (19).

Based on these results (19), we undertook this pilot study to examine the safety and effects of a non-selective beta-blocker, nadolol, in subjects with mild asthma (20). To our knowledge,

this is the first study that investigated the safety and effect of chronic administration of a non-selective beta-blocker for the potential treatment of human asthma.

Material and Methods

Design

This was an 11-week, prospective, open-label, dose-escalation pilot study. The main objective of the study was to evaluate the safety of the non-selective beta-blocker, nadolol, in subjects with mild asthma. Secondary objectives were to evaluate the effects of chronic treatment with nadolol on airway hyperresponsiveness, pulmonary function and asthma control. The study was performed at Baylor College of Medicine (BCM). The BCM Institutional Review Board approved this study and all subjects gave written informed consent prior to being enrolled in the study. An IND approval to study nadolol in asthma was also obtained from the U.S. Food and Drug Administration.

Study Subjects

Subjects with a diagnosis of asthma were recruited for this study if they met the following clinical criteria: age between 18–50; non-smokers or past smokers with <10 pack.year tobacco consumption; baseline pre-bronchodilator forced expiratory volume at 1 sec (FEV1) \geq 80% of the predicted value; and in whom methacholine produced a reduction in FEV1 of 20% (PC20 methacholine) at concentrations <8 mg/ml. Subjects also had to have a baseline blood pressure \geq 110/70 mmHg and pulse rate \geq 60 bpm. Subjects were excluded if: they had other significant health issues, if they had used, or were using, any controller medication (oral or inhaled corticosteroids, leukotriene modifiers or long-acting beta₂-AR agonists) within 4 weeks of the first baseline visit. Also excluded were those who were taking any beta-blocker medications, those with a history of a life threatening asthma (intubations, respiratory failure or intensive care unit admission for asthma), and those with a history of upper/lower respiratory tract infection or asthma exacerbation within 6 weeks of first baseline visit.

Methods

Eligible subjects were in the study for an 11-week period, during which they received the study medication for 9 weeks. Following a two weeks run-in period, subjects who remained eligible entered a dose-escalation phase of the study lasting up to 6 weeks, followed by a 3-week dose maintenance period (Figure 1). Nadolol (Corgard®, Monarch Pharmaceuticals) was administered orally once daily in the morning. The initial dose of nadolol given at visit two (V2) was 10 mg. At each of the subsequent weekly visit (V3 - V8) the dose was escalated, maintained or reduced using pre-determined criteria. These criteria were based on the magnitude of change in FEV1, PEFr, change in the use of rescue medication and blood pressure and pulse measurements. If a subject could not be escalated two weeks in a row using the pre-set criteria, the current dose of study medication was defined as the maximum permitted dose (MPD). Once the MPD was established, the subject was maintained on that dose for the remainder of the study. Albuterol + ipratropium bromide combination (Combivent®, Boehringer Ingelheim) metered dose inhaler was used throughout the study as rescue medication. Spirometry was performed every visit and was performed every 30 minutes for 4 hours following the initial administration of the first and each subsequent escalated dose of nadolol. Bronchoprovocation tests were performed at baseline, and at V3 and V9. The dilution scheme used for methacholine inhalation challenge tests was performed using the American Thoracic Society Guidelines for Methacholine Challenge Testing (21). Study subjects were asked to withhold their rescue medication at least 12 hours prior to the study visit. Blood pressure and pulse measurements were measured every visit and every 30 minutes for 4 hours during the first nadolol dose and dose escalation visits. Asthma control scores were calculated every visit using the Juniper Asthma Control Score questionnaire (ACQ) (22). In addition,

each subject kept a daily diary with measurement of morning peak expiratory flow rates and rescue medication use, and any other new symptoms.

Statistical Analysis

When comparing the effects of drug treatment on baseline parameters, a paired two-sided student's t-test was performed. When comparing the effects of different doses for differences from baseline or among the effects of the different doses, a two-way ANOVA was performed and a Bonferroni post-hoc test was used. To determine if there was a relationship with nadolol dose and the observed effects on PC₂₀ and FEV1 a least squares linear regression analysis was performed. The results were considered significant if $p \leq 0.05$.

Results

Ten subjects fulfilled the inclusion criteria and were enrolled in the study. All subjects completed the 11 weeks of the study. Subjects' demographics and baseline characteristics are shown in Table 1. The change from baseline in study parameters monitored are shown in Table 2.

Safety and Maximal Permitted Dose

As previously mentioned the dose of nadolol was escalated based on preset cardiovascular and pulmonary safety parameters. In three subjects, 10 mg was the maximum permitted dose achieved, four subjects achieved 20 mg daily dose, and 3 other subjects tolerated a 40 mg daily dose as their maximum permitted dose. Table 3 lists the specific clinical circumstances that limited dose escalation in subjects. It should be noted that all subjects were completely asymptomatic of the criteria that prevented their dose escalation; subjects whose FEV1 was the limiting factor had no respiratory complaints such as difficulty breathing, and those in which falls in blood pressure was the limiting factor had no episodes of dizziness or postural hypotension. Compared to baseline values, there were no significant changes with chronic nadolol treatment in asthma control (ACQ scores), PEFr, use of rescue medication, or in blood pressure (Table 2). There was a reduction in mean heart rate that bordered on statistical significance ($p = 0.051$).

Airway Hyperresponsiveness

We observed a dose-dependent significant attenuation in airway hyperresponsiveness (PC₂₀ methacholine) from baseline in eight out of ten subjects. This was seen in all seven subjects who were able to be dose escalated to the 20 and 40 mg daily doses (Figure 2A). Figure 2B shows this change in PC₂₀ expressed as doubling doses of the methacholine concentration. All seven subjects that were able to be dose-escalated above 10 mg daily dose of nadolol had a greater than one doubling dose shift in their PC₂₀ methacholine (Figure 2B) (mean of 1.8 ± 0.16 doubling doses). Furthermore, a positive correlation between the nadolol dose and the change in PC₂₀ methacholine ($r = 0.86$; $p=0.0016$) (Figure 3) was also observed. Despite being asymptomatic, two patients experienced a reduction in their PC₂₀ methacholine.

Lung Function

The acute effects of the first dose of nadolol on forced expiratory volume at 1 sec (FEV1) are shown in Table 4. Four subjects had a >10% fall in FEV1 in the 4 hours following the initial administration of nadolol. However, during subsequent visits, the majority of the subjects met the criteria for dose escalation (7 of the 10 subjects). We observed a significant decrease in mean FEV1 from baseline (5%) when all the doses were pooled ($p<0.05$). However, there was no significant correlation between the maximum dose of nadolol used and the fall in FEV1. ($r = -0.49$, $P = 0.15$).

Discussion

To our knowledge, this is the first study examining the safety and effects of the chronic administration of a non-selective beta-blocker in subjects with asthma. Non-selective beta-blockers such as the one used in this trial, nadolol, are currently contraindicated in patients with asthma. However, the results from this small pilot study in subjects with mild asthma suggest that when using an escalating dose strategy, the drug is well tolerated and produces a dose-dependent decrease in airway hyperresponsiveness to methacholine by most subjects. Eight of the 10 subjects in our study, including all 7 who were dose escalated to >10 mg, had an improvement in their PC₂₀ methacholine dose with a mean change of 1.8 ± 0.14 doubling doses. This magnitude of the shift in PC₂₀ methacholine is significant and within the range produced by other disease modifying therapies, including chronic inhaled corticosteroid administration (23-26). The positive response rate of 8 of 10 is also very similar to that reported in small pilot trials with inhaled corticosteroids (23,25,26). However, two patients who were on the lowest dose of nadolol (10 mg), had a decrease in their PC₂₀ methacholine.

The rationale for this study was the consistency of the analogy between CHF and asthma with regards to the use and outcomes of beta-AR drugs (27,28). Admittedly, asthma and CHF are different diseases, but if one limits their focus to the qualitative and temporal results with regard to beta-AR ligands, then there is a compelling analogy between the two diseases (28). In both diseases, the acute use of agonists improves symptoms, while acute use of antagonists can worsen symptoms, and chronic use of agonists can worsen symptoms, while chronic use of certain antagonists, at least in CHF, cause a highly significant reduction in mortality and an improvement of symptoms (12,13,17,18).

There has been a long-term controversy about the safety of the chronic use of beta₂-AR agonist in asthma. This controversy has involved the regular use of short-acting beta₂-AR agonists such as albuterol, fenoterol and isoproteronol (29-31), as well as long-acting beta₂-AR agonists such as salmeterol and formoterol (32-35). The controversy has also implicated high efficacy beta₂-AR agonists such as isoproteronol and fenoterol (36-38), as well as low efficacy partial beta₂-AR agonists such as salmeterol (7). The results of some of these studies have prompted the U.S. Food and Drug Administration to request a 'black box' warning on all beta₂-AR (39). While several hypotheses have been proposed to explain the negative outcomes with chronic beta₂-AR agonists in the various studies (too high a dose, improper randomization of subjects, lack of concurrent steroid use, etc.,) there is no doubt that chronic use of this class of drugs has a 'cloud' of reported undesired effects.

Based on the CHF experience, we hypothesized that the short- and long-term response of certain beta-blockers would also be different. This theory, that the observed beta₂-AR ligand response was determined by the duration of exposure to the beta₂-AR ligand, was previously tested and verified in a murine model of asthma (19). The results of that study, coupled with our analogy to CHF, led to this pilot study in humans which is the first-time the chronic effect of a non-selective beta-AR 'blocker' (more specifically, a beta₂-AR inverse agonist) has been studied in asthmatics (20).

The protocol for this trial allowed testing of only mild asthmatics, and had very rigorous cardiovascular and pulmonary function parameters that had to be met prior to dose escalation. In 6 of the 10 subjects, the limiting factor preventing dose escalation were falls in blood pressure and/or heart rate below the acceptable parameters (blood pressure of at least 110/70 mmHg and heart rate of at least 60 bpm).

As noted earlier, the first dose of nadolol (10 mg) produced a fall in FEV₁ of > 10% in 4 of the 10 subjects. This early adverse effect has also been observed when first administering beta-blockers to CHF patients (15). To minimize these initial adverse effects, future studies will use

a lower initial dose as well as an extended time between dose escalations. These changes will make the protocol more consistent with the successful titration schedule used in CHF. Additional strategies to reduce the initial adverse effects will include co-administration of rescue medications such as anticholinergic agents and/or beta₂-AR agonists. Indeed, based on data suggesting that chronic beta₂-AR agonist activation up-regulates phospholipase C-beta1 (PLC-beta1), the enzyme used by most spasmogens to elicit bronchoconstriction (40), Liggett and McGraw have recently hypothesized that, “Antagonists to these receptors [beta₂-ARs] might be able to act synergistically with chronic beta-agonists to block the effect of PLC” (41). Also, anticholinergic agents have been shown to be effective in reversing beta-blocker induced bronchospasm, and therefore would be another candidate for co-administration (42). Finally, reformulation of the drug to produce slower time peak and less peak to trough ratios may also reduce the initial adverse effects, and a formulation for inhaled delivery may minimize cardiovascular effects.

Two subjects in our study experienced deteriorations of their PC₂₀ methacholine value at the lowest dose used (10 mg) that persisted to the end of the study. The same two subjects also experienced the largest fall in FEV₁ after the 9 weeks of treatment, and it was these two subjects who received the absolute lowest chronic dose of nadolol on a mg/kg basis (0.13 and 0.14 mg/kg, while the next lowest was 0.17 mg/kg). Future work will need to explore further the characteristics of subjects who may be at higher risk of deterioration with the use of beta-blockers. Such risk factors may be related to genetic polymorphisms of the beta-AR which in turn affect the response to the beta₂-AR inverse agonist, nadolol, as is the case that some polymorphisms may affect the response to the regular use of beta₂-AR agonists (43,44). On the other hand, it may simply be that a response rate of about 80% is as high as one can expect in these small pilot trials which was the case with the response observed with the use of inhaled corticosteroids which has also been about 80% for comparably sized trials (23,25,26).

The shift in airway hyperresponsiveness observed in this study is comparable to the shifts observed in other some clinical trials with chronic inhaled corticosteroids (23-26) and is regarded as clinically significant. Sont and colleagues showed that guiding treatment with inhaled corticosteroids to improve airway hyperresponsiveness in addition to optimizing symptoms and lung function leads to more effective control of asthma while alleviating chronic airways inflammation (45). Furthermore, our observation of a positive correlation between the nadolol dose and the magnitude of the change in PC₂₀ suggests this response was a result of drug treatment and not a placebo effect.

We observed a small but statistically significant decrease in FEV₁ from baseline in the pooled data with chronic nadolol therapy (5%, p<0.05). However, the change in FEV₁ from baseline was not significant in the 7 subjects who tolerated a > 10 mg daily dose of nadolol. Nevertheless, improvement in FEV₁ is also regarded as an important endpoint in demonstrating efficacy of a new asthma medication. However, in the current study design such improvements would be difficult to observe because baseline FEV₁ for these patients was 90% of predicted leaving little room for viewing any positive efficacy signal on lung function.

Our study has several limitations including the small number of subjects, its open label design and the absence of a placebo group. Because this was a pilot study with safety as the primary outcome, we could only enroll subjects with mild disease who had minimal symptoms. The effect in symptomatic subjects with more severe asthma need to be explored in future larger studies.

In summary, this open label pilot study evaluated a novel hypothesis – that the dose-escalating administration of a non-selective beta-blocker (with beta₂-AR inverse agonist properties), a drug currently contraindicated in patients with asthma, may be well tolerated and may have a

beneficial effect by most subjects with mild asthma when administered chronically. This hypothesis began as a theoretical proposal (27,28), proceeded into an animal model of asthma (19), and now tested in a small pilot study in humans. Although the results are very preliminary and limited by the weaknesses outlined above, we believe they clearly warrant more testing.

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Abbreviations

CHF, congestive heart failure; PLC, phospholipase C; PC20, provocative concentration reduction in FEV1 of 20%; beta₂-AR, beta₂-adrenoceptor; FEV1, forced expiratory volume at 1 sec; PEFr, peak expiratory flow rate; V, visit; MPD, maximum permitted dose; ACQ, asthma control questionnaire ..

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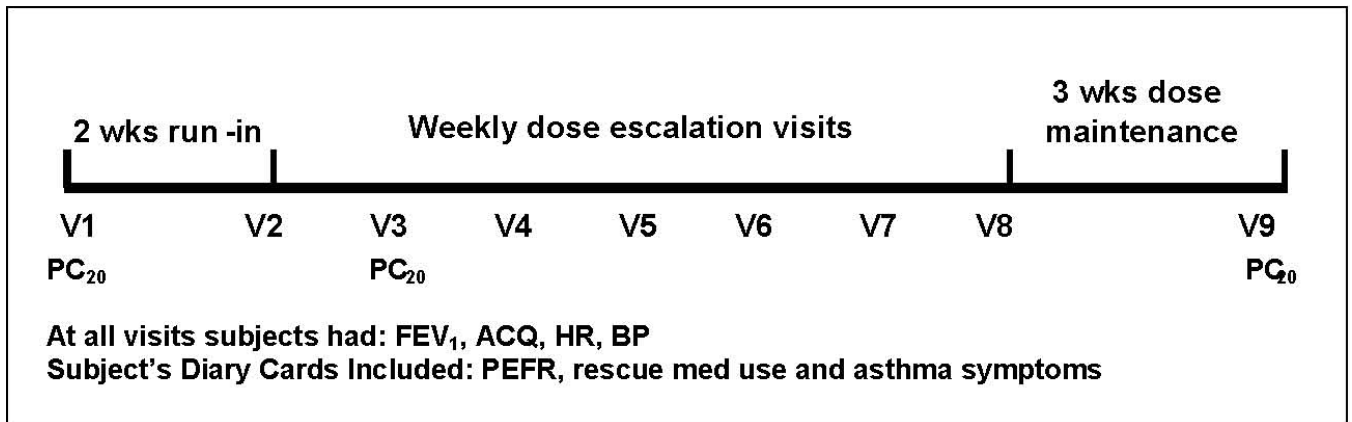
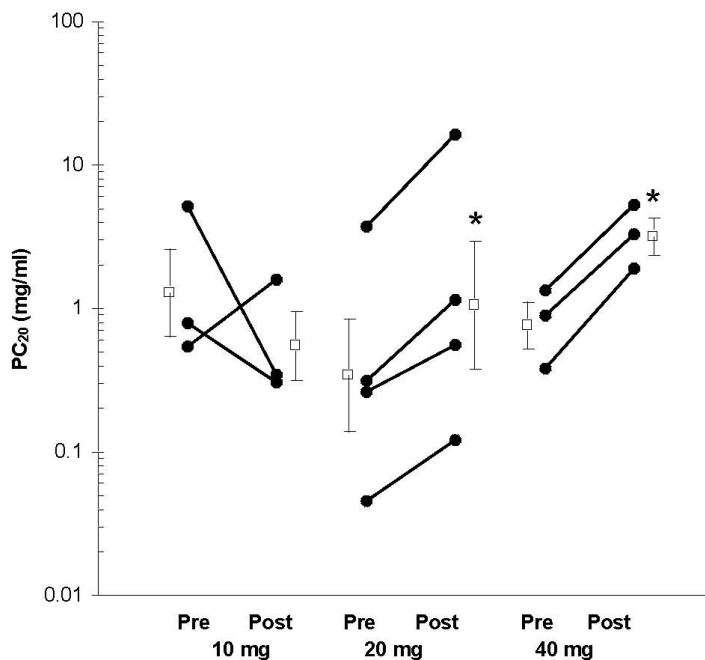


Figure 1. Schematic description of study protocol

V = Visit, ACQ= Asthma Control Questionnaire Score, PEFr = peak expiratory flow rates, PC₂₀: provocative concentration of methacholine producing a 20% fall in FEV₁, HR = heart rate, BP = Blood pressure.

A.



B.

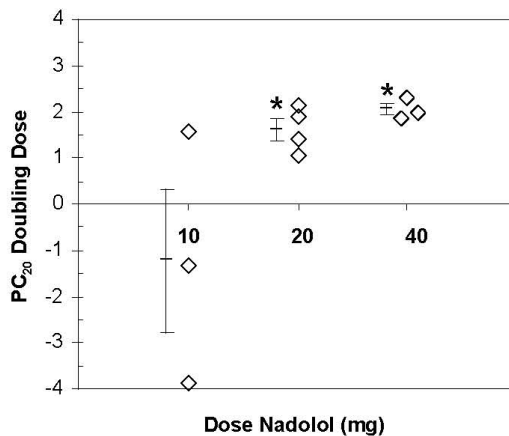


Figure 2A & 2B. The effect of chronic treatment with nadolol on the PC₂₀ methacholine in mild asthmatic patients

A. Data shown as pre- and post-treatment with final nadolol doses of 10, 20, and 40 mg. Mean values ± SEM are also shown. Comparisons between pre- and post-treatment with nadolol were done using paired t-test. *P<0.05. **B.** Data for each patient shown as the doubling dose in PC₂₀ methacholine values between baseline and after treatment relative to final doses of nadolol of 10, 20, and 40 mg. Mean values ± SEM are also shown.

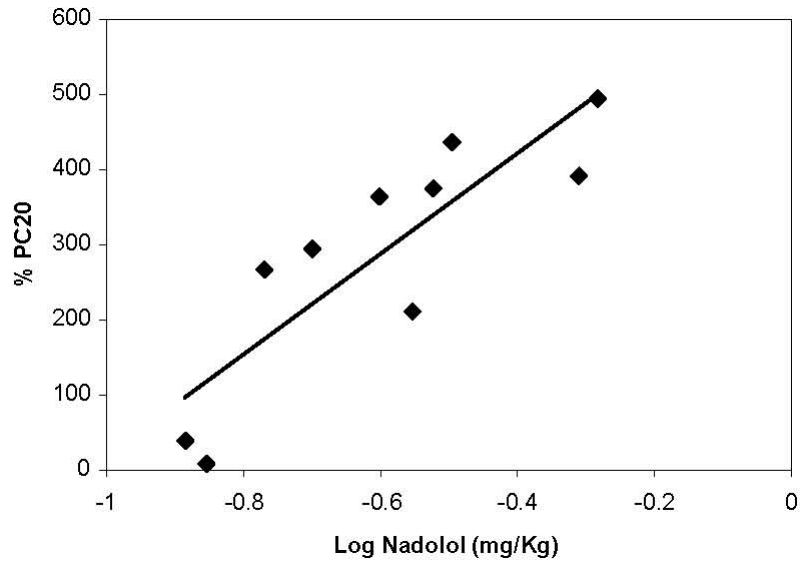


Figure 3. Correlation Between Nadolol Dose and Change in PC₂₀

Correlation between nadolol dose log (mg/Kg) versus the percentage of change in PC₂₀ as compared with baseline levels for each patient. Least squares linear regression correlation: $r = 0.86$; $p=0.0016$

Table 1

Baseline Demographics and Characteristics of Study Participants

Subject No.	Gender	Age (yr)	Race	FEV ₁ (% predicted)	PC20 (mg/ml)
1	M	23	Black	88	0.773
2	F	28	White	91	0.259
3	M	40	White	84	0.380
4	F	45	White	84	1.329
5	F	28	Black	128	0.305
6	M	47	Black	80	0.884
7	M	32	White	85	5.025
8	F	37	Black	83	0.045
9	F	22	White	91	3.667
10	F	27	Asian	86	0.538
Mean		32.9		89.9	0.64 ^A
SEM		2.8		4.4	1.54 ^B
Range		22 – 47		80 – 128	0.045 – 5.025

^A Geometric mean^B Geometric standard error of mean

Table 2
Effects of Chronic Nadolol Administration on Pulmonary and Cardiovascular Parameters

Parameter Measured	Baseline Mean (SEM)	Final Mean (SEM)	MPD	<i>p</i> value ^C
FEV1 % Pred	89.9 (4.4)	84.5 (4.1)	All	< 0.01
	86.2 (1.1)	76.2 (3.2)	10 mg	
	100.7 (10.0)	95.5 (8.0)	20 mg	
	82.5 (1.4)	79.8 (1.3)	40 mg	
PC ₂₀ (mg/ml)	1.32 (0.53)	3.03 (1.52)	All	0.0063 0.0042
	2.11 (0.74)	1.46 (0.39)	10 mg	
	1.07 (0.87)	4.45 (3.86)	20 mg	
	0.86 (0.27)	3.43 (0.96)	40 mg	
ACQ	1.54 (0.26)	1.46 (0.21)	All	
	1.90 (0.64)	1.67 (0.50)	10 mg	
	1.47 (0.40)	1.14 (0.33)	20 mg	
	1.28 (0.44)	1.62 (0.37)	40 mg	
PEFR (L/min)	437 (27)	433 (28)	All	
	422 (40)	414 (52)	10 mg	
	423 (42)	421 (44)	20 mg	
	471 (68)	468 (61)	40 mg	
Rescue Med Use Puffs / Day	1.8 (0.5)	2.0 (0.6)	All	
	1.7 (1.2)	0.6 (0.4)	10 mg	
	1.7 (0.4)	2.2 (0.8)	20 mg	
	2.1 (1.3)	3.3 (1.2)	40 mg	
Heart Rate (bpm)	76 (1)	69 (4)	All	0.051
	72 (3)	65 (6)	10 mg	
	79 (1)	74 (8)	20 mg	
	77 (1)	66 (7)	40 mg	
Blood Pressure (mmHg)	119/75 (4/2)	116/74 (6/2)	All	
	115/70 (3/0)	108/73 (7/2)	10 mg	
	116/74 (2/2)	106/67 (5/2)	20 mg	
	128/80 (11/4)	138/84 (9/7)	40 mg	

^C Only $p \leq 0.05$ values are provided except for heart rate. All the remaining comparisons were not significant. ACQ = Asthma Control Score, MPD= Maximal Permitted Dose

Table 3

Maximal Permitted Dose (MPD) of Nadolol and Limiting Factor(s) for Dose Escalation

Subject No.	Final Dose Nadolol (mg)	Reason
1	10	FEV1
2	20	BP
3	40	HR
4	40	Rescue Med
5	20	BP and HR
6	40	HR
7	10	FEV1
8	20	FEV1
9	20	BP
10	10	BP and HR

Table 4**Effects of First Dose of Nadolol (10 mg) on Lung Function**

Shown is the greatest change seen over the first four hours (monitoring every 30 min) following oral administration of 10 mg nadolol.

Subject No.	% Change from baseline FEV ₁
1	-7.9
2	-12.4
3	1.4
4	-5.9
5	-13.2
6	0
7	-18
8	-18
9	-0.6
10	0.8
Mean	-7.4
(SEM)	2.4
Range	-18 to 1.4