

The inverse agonist propranolol confers no corticosteroid-sparing activity in mild-to-moderate persistent asthma

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Abstract

The murine asthma model shows that switching off airway β_2 receptors with an inverse agonist may confer anti-inflammatory effects as well as corticosteroid-sparing activity. We have assessed for any corticosteroid-sparing effects of propranolol, an inverse agonist, added to low-dose inhaled corticosteroid (ICS) compared with higher dose ICS. A randomized double-blind placebo-controlled cross-over trial in mild-to-moderate persistent asthmatic patients was performed. After a run-in (2 weeks) on hydrofluoroalkane-beclometasone dipropionate (HFA-BDP) at 100 $\mu\text{g}/\text{day}$ (HFA-BDP100), patients received randomized treatments (4 weeks) with propranolol at 80 mg/day plus HFA-BDP at 100 $\mu\text{g}/\text{day}$ compared with placebo plus HFA-BDP at 400 $\mu\text{g}/\text{day}$ (HFA-BDP400). Propranolol was up-titrated to 80 mg/day over the initial 2 weeks. Tiotropium was co-administered until 5 days before each histamine challenge (the primary outcome). Sixteen patients completed the study [mean age, 38 years; forced expiratory volume in 1 s (FEV_1), 86.4%; histamine provocative concentration causing a 20% fall in FEV_1 (PC_{20}), 1.39 mg/ml; ICS dose, 406 $\mu\text{g}/\text{day}$]. Histamine PC_{20} was unchanged by adding propranolol to HFA-BDP100 compared with baseline (HFA-BDP100) {0.17 doubling dilution (dd) difference [95% confidence interval (CI): -0.58 to 0.92]}, but there was a significant improvement with HFA-BDP400 compared with both baseline [1.05 dd (95% CI: 0.43 – 1.66); $P=0.02$], and propranolol+HFA-BDP100 [0.88 dd (95% CI: 0.45 – 1.30); $P=0.006$]. Significant improvements were also observed with HFA-BDP400 for exhaled nitric oxide, blood eosinophils, serum eosinophilic cationic protein and asthma quality-of-life questionnaire symptoms compared with propranolol + HFA-BDP100. Salbutamol recovery post-challenge was partially blunted by propranolol (median prolongation 5 min; $P=0.002$). Domiciliary evening FEV_1 also fell with propranolol+HFA-BDP100 [mean reduction from baseline 0.22 litres (95% CI: 0.10 – 0.34); $P=0.012$], whereas Asthma Control Questionnaire remained unchanged. In conclusion, the inverse agonist propranolol produced no improvements when given with low-dose ICS, whereas further significant improvements in airway hyper-responsiveness and inflammation were demonstrated with higher dose ICS. Thus, propranolol does not confer corticosteroid-sparing activity in persistent asthma.

Key words: airway hyper-responsiveness, asthma, β -blocker, corticosteroid, histamine

INTRODUCTION

Current asthma treatment advocates a step-wise approach, with inhaled corticosteroids (ICSs), the main anti-inflammatory controller therapy, and long-acting β_2 agonists (LABA), the preferred second-line bronchodilator add-on therapy [1]. However, despite optimizing ICS/LABA, many patients remain poorly controlled

[2]. Inevitably, some patients require higher ICS dosing, highlighting the unmet need for new ICS-sparing strategies.

We would not expect any novel asthma therapy to come in the guise of a drug long-considered hazardous in asthmatic patients due to the risk of profound acute bronchoconstriction [3]; nevertheless, β -blockers have been the subject of recent interest and study in this regard. Murine asthma models demonstrated

Abbreviations: ACQ, Asthma Control Questionnaire; AHR, airway hyper-responsiveness; AQLQ, Asthma Quality of Life Questionnaire; ATS, American Thoracic Society; B2ADR, β_2 adrenoceptor; BP, blood pressure; bpm, beats per min; CI, confidence interval; CV, coefficient of variation; dd, doubling dilution; ECP, eosinophilic cationic protein (serum); F_2NO , fraction of exhaled nitric oxide; FEV_1 , forced expiratory volume in 1 s; FVC, forced vital capacity; HFA-BDP, hydrofluoroalkane-beclometasone dipropionate; HR, heart rate; ICS, inhaled corticosteroid; IOS, impulse oscillometry; LABA, long-acting β_2 agonist; OUCC, overnight urinary cortisol/creatinine ratio; PC_{20} , provocative concentration causing a 20% fall in FEV_1 ; ppb, parts per billion; R5, total airway resistance at 5 Hz; R5-R20, peripheral airway resistance subtracting resistance at 20 Hz from R5.

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improvements in airway hyper-responsiveness (AHR) [4], up-regulation of β_2 adrenoceptors (B2ADRs) [4,5] and a reduction in airway inflammation following chronic β -blockade with nadolol [6]. Moreover, in humans, open-label chronic nadolol therapy in steroid-naïve asthmatic patients [7,8] resulted in significantly improved AHR, achieving a 1.8 doubling dilution (dd) increase in methacholine PC₂₀ [provocative concentration causing a 20% fall in forced expiratory volume in 1 s (FEV₁)], almost twice the minimum important difference [9].

Regarding the pivotal safety issue of using β -blockers in asthma, there was no adverse signal from a meta-analysis of chronic β -blocker studies in patients with reactive airways disease for FEV₁, symptoms or reliever use [10]. Prospective open-label studies by Hanania et al. [8] and Short et al. [11] have shown that the response to high-dose salbutamol rescue was only partially blunted post-bronchial challenge in asthmatic patients receiving either chronic nadolol or single-dose propranolol respectively, with only minor FEV₁ reductions.

We have published data recently showing no additional therapeutic benefit of chronic propranolol compared with placebo when added to medium-dose ICS on AHR to either histamine or methacholine [12]. This was surprising given the marked effect seen in ICS-naïve patients using nadolol; however, this could perhaps be explained by the fact that ICSs themselves act through both up-regulation of airway B2ADRs [13] as well as being first-line anti-inflammatory treatment for asthma, therefore, leaving no room for further improvement.

The next logical question, therefore, is whether there may be any corticosteroid-sparing effect of chronic β -blockade on AHR and other inflammatory outcomes in asthma. This hypothesis is supported by data showing steroid-sparing properties of nadolol using the mouse asthma model [14]. In this follow-on study, we examined whether chronic propranolol treatment added to low-dose ICS was non-inferior to increasing the dose of ICS alone on the primary outcome of histamine AHR in persistent asthmatic patients, that is specifically testing for a corticosteroid-sparing effect.

This work was presented at the British Thoracic Society Winter meeting, held in London, U.K., on 4–6 December 2013, and subsequently published in abstract form [14a].

MATERIALS AND METHODS

Patients

Stable histamine-responsive (PC₂₀ < 8 mg/ml) persistent asthmatic patients receiving $\leq 1000 \mu\text{g/day}$ of ICS (beclometasone dipropionate equivalent) were enrolled (Figure 1). The main exclusion criteria were the following: uncontrolled asthma symptoms; FEV₁ < 60% predicted; resting systolic blood pressure (BP) < 110 mmHg; resting heart rate (HR) < 60 beats per min (bpm); any degree of heart block assessed by ECG; current use of negatively chronotropic medication; asthma exacerbation requiring oral steroid use in previous 6 months; and pregnancy.

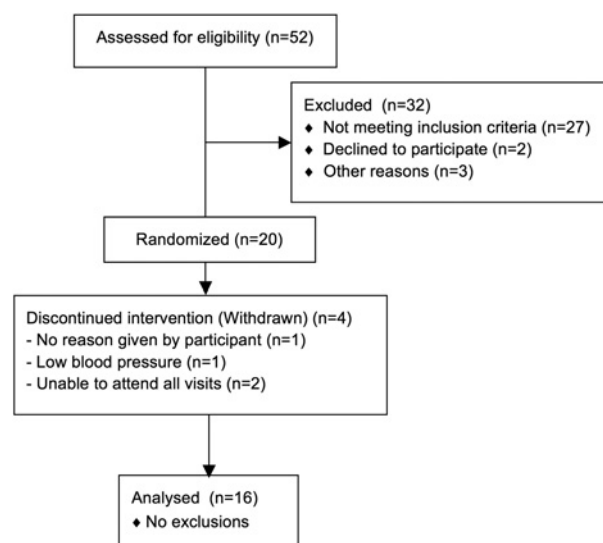


Figure 1 CONSORT diagram of patient recruitment

Design

The design was a single-centre randomized double-blind placebo-controlled cross-over study. Following a 2-week run-in with hydrofluoroalkane-beclometasone dipropionate (HFA-BDP; Qvar® Easibreathe, TEVA Pharmaceuticals) at 100 $\mu\text{g/day}$, ex-valve dose (80 μg ex-actuator), patients were randomized to either (i) HFA-BDP at 100 $\mu\text{g/day}$ plus propranolol sequentially up-titrated from 10 mg bid (1 week) to 20 mg bid (1 week) and then 80 mg (sustained release) od (2 weeks); or (ii) HFA-BDP at 400 $\mu\text{g/day}$, ex-valve dose (320 μg ex-actuator), plus matched placebo for 4 weeks (Figure 2). Participants commenced tiotropium at 18 μg od (Spiriva® Handihaler, Boehringer Ingelheim) at the beginning of run-in and both treatments, to mitigate against potential bronchoconstriction upon initial propranolol exposure [15], and then discontinued 5 days prior to each histamine challenge.

Patients were monitored in our department for 2 h following administration of the first dose of propranolol (or placebo) at visits 1 and 3, with safety measurements (HR, BP and FEV₁) assessed prior to up-titration to 80 mg of propranolol (or placebo) at visits 2 and 4. At the end of the first randomized treatment arm, patients were crossed over directly to the remaining treatment arm.

Alongside initial ICS step-down, patients withheld any concomitant LABA or other third-line asthma therapy, including antihistamines for 1 week prior to run-in and for the duration of the study.

The primary outcome was histamine PC₂₀ comparing post-run-in baseline with completed treatment periods. Secondary outcome measures were the following: spirometry, impulse oscillometry (IOS), fraction exhaled nitric oxide (F_ENO), blood eosinophils, serum eosinophilic cationic protein (ECP), overnight urinary cortisol/creatinine ratio (OUCC); pre-/post-histamine challenge measurements (HR, BP, serum potassium and FEV₁),

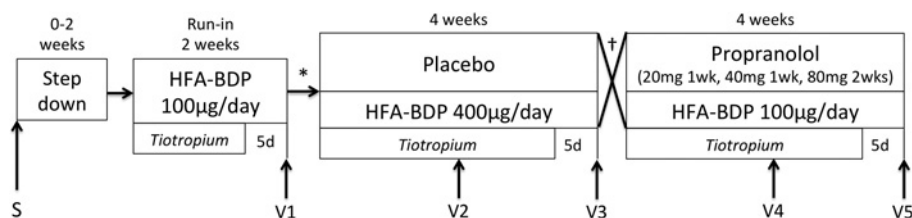


Figure 2 Study flow diagram

Screening visit (S). Tiotropium stopped 5 days (5d) prior to histamine challenges at main study visits 1, 3 and 5 (V1, V3 and V5). Patients randomized (*) at V1. Cross-over (†) to remaining treatment arm. Safety visits at 2 weeks into treatment periods (V2 and V4). Study complete at end of V5.

domiciliary FEV₁, Asthma Quality of Life (AQLQ) and Asthma Control Questionnaires (ACQ).

St. Mary's Pharmaceutical Unit, Cardiff, Wales, U.K., performed the blinding and randomization of the investigational medicinal products.

Measurements

Histamine was dispensed via nebulized solution (Tayside Pharmaceuticals), and the challenge was performed in accordance with standard guidelines. A dosimeter (Markos-Mefar) was used with doubling concentrations of histamine from 0.3125 mg/ml to 40 mg/ml. The PC₂₀ was then calculated by computer-assisted log-linear interpolation of the dose response. Nebulized albuterol (5 mg) was used to recover patients immediately post-challenge. FEV₁ was measured every 5 min for 30 min post-challenge or until it returned to within 5% of baseline. If FEV₁ had not recovered by 15 min, nebulized ipratropium bromide (500 µg) was administered additionally. HR and serum potassium were measured pre-challenge and 15 min post-albuterol administration. All HR and BP measurements were recorded in triplicate. Exhaled tidal nitric oxide was measured in line with the American Thoracic Society (ATS) recommendations [16] using a NIOX analyser (NIOX[®] Nitric Oxide Monitoring System, Aerocrine AB) prior to other pulmonary function measurements. Impulse oscillometry (Masterscreen IOS) was performed in accordance with the manufacturer's guidelines. Spirometry was performed using a SuperSpiro (Carefusion) according to the ATS guidelines [17]. Domiciliary FEV₁ was performed in triplicate in both the morning and evening, using a handheld PiKo monitor (n-Spire Health) according to the manufacturer's instructions. Peripheral blood eosinophils were measured using the Sysmex XE2100 Hematology auto-analyser. Serum ECP was measured in duplicate using a UniCAP system (Phadia) with a coefficient of variation (CV) of 3%. Overnight urine was collected between 22.00 h and 08.00 h. Urinary free cortisol was measured using a commercial RIA kit (DiaSorin). The intra-assay CV was 21%, with the inter-assay CV of 13%. Urinary creatinine was measured using the RATE technique on a Cobas-Bio auto-analyser (Roche Products), with an inter-assay CV of 4.3%. Skin prick testing was performed using standard allergen extracts (Diagenics).

Statistical analyses

All data were assessed for normality of distribution. Non-normally distributed variables were logarithmically transformed or analysed non-parametrically. The null hypothesis was that, compared with post-run-in baseline on HFA-BDP at 100 µg/day, adding propranolol at 80 mg/day confers no change to histamine PC₂₀, whereas increasing the dose of HFA-BDP alone (400 µg/day) causes a significant improvement (positive control). To detect a minimal important difference of 1 dd in histamine PC₂₀ between randomized treatments, assuming a within-subject S.D. of 1.3 dd, required 16 participants to achieve 80% power with an α error of 0.05 (two-tailed) using a cross-over design (matched subjects). Analysis was performed using repeated-measures ANOVA, factoring treatment and sequence effects, followed by Bonferroni's correction for all pairwise comparisons ($P < 0.05$, two-tailed). All analyses were performed using IBM SPSS v20.

Ethics

The East of Scotland Research Ethics Service granted ethical approval (Ref: 11/ES/0031). All patients provided written informed consent. The study was registered at ClinicalTrials.gov with study ID NCT01544634.

RESULTS

Participants

Sixteen patients completed per protocol (Table 1 and Figure 1). Mean FEV₁ was 86.4% predicted (95% CI: 80.9–91.9) and the geometric mean histamine PC₂₀ was 1.39 mg/ml (95% CI: 0.93–2.07) at screening. There were no significant adverse events.

Airway hyper-responsiveness

The primary outcome, histamine PC₂₀, showed no significant difference, adding propranolol to low-dose HFA-BDP at 100 µg/day compared with post-run-in baseline on HFA-BDP at 100 µg/day alone [mean difference 0.17 dd (95% CI: –0.58 to 0.92)] (Table 2 and Figure 3A). There was, however, a significant improvement in PC₂₀ with higher dose HFA-BDP at 400 µg/day and placebo compared with both baseline [1.05 dd (95% CI: 0.43–1.66); $P = 0.02$], and propranolol [0.88 dd (95% CI: 0.45–1.30); $P = 0.006$] (Figure 4).

Table 1 Demographics of the subjects

Data are presented as means (95% CI) or absolute values unless otherwise stated. *Medians (interquartile range). †Geometric means (95% CI). BDP ICS, beclometasone dipropionate equivalent ICS dose; BMI, body mass index; FEF₂₅₋₇₅, forced expiratory flow between 25–75% of forced vital capacity; LTRA, leukotriene receptor antagonist; SPT, skin prick test to allergen.

Variable	n = 16
Age (years)	38 (31, 44)
Gender (n) (male:female)	6:10
BMI (kg/m ²)	26.9 (24.6, 29.2)
Atopy (>1 SPT positive; n)	14
SPT positivity*	2.5 (1, 4)
BDP ICS (μg/day)	406 (243, 569)
LABA (all combined with ICS; n)	7
Antihistamine/LTRA (n)	2/2
FEV ₁ (% predicted)	86.4 (80.9, 91.9)
FEF ₂₅₋₇₅ (% predicted)	53.6 (46.5, 60.7)
R5 (% predicted)	151 (126, 181)
R5–R20 (kPa/litre per s)	0.13 (0.07, 0.19)
F _E NO (ppb)†	40 (29, 55)
Histamine PC ₂₀ (mg/ml)†	1.39 (0.93, 2.07)
Systolic BP (mmHg)	131 (122, 140)
Diastolic BP (mmHg)	79 (73, 84)
HR (bpm)	73 (68, 78)

Cardiovascular effects and salbutamol recovery

Propranolol produced significant effects on other outcomes – 80 mg/day caused significant reductions from baseline in both supine HR by approximately 10 bpm ($P < 0.001$) and supine BP after chronic dosing (Table 2). Furthermore, recovery time

to within 5% of baseline FEV₁ post-salbutamol was blunted significantly by propranolol compared with both baseline and placebo (median prolongation 5 min; $P = 0.002$) (Table 3 and Figure 5A), as was post-recovery FEV₁ [mean reduction 6.4% (95% CI: 3.7–9.1%) from baseline; $P = 0.001$] (Table 3 and Figure 5D). Three patients on propranolol required ipratropium bromide 15 min post-salbutamol to fully recover post-challenge, compared with no patients following baseline or placebo challenges ($P = 0.05$). All active propranolol patients had recovered by 25 min post-salbutamol. There was no salbutamol-induced fall in serum potassium post-challenge with propranolol, compared with significant reductions after baseline ($P < 0.001$) and placebo ($P = 0.002$) challenges (Table 3 and Figure 5C). As similar significant blunting of the response was seen in post-challenge HR and BP measurements with propranolol (Table 3 and Figure 5B) compared with baseline and placebo.

Inflammation

We have also assessed local and systemic inflammatory outcomes, including F_ENO, blood eosinophilia and serum ECP, finding no significant difference in any outcome with propranolol compared with baseline. However, there were significant reductions with high-dose ICS plus placebo compared with baseline for both F_ENO ($P = 0.02$) (Table 2) and eosinophil levels ($P = 0.03$) (Table 2 and Figure 3C). Serum ECP was significantly lower with high dose ICS plus placebo compared with propranolol ($P = 0.01$) (Table 2 and Figure 3D).

Symptoms and asthma control

Propranolol did not cause any significant change in AQLQ or ACQ over baseline values (Table 2). High-dose ICS did lead to significant improvements in the AQLQ symptom component

Table 2 AHR, local and systemic inflammation, pulmonary function, adrenal function, asthma control and cardiovascular outcomes

All data are presented as means (95% CI) unless otherwise stated. *Geometric means (95% CI). Overall significance with repeated-measures ANOVA. Significant ($P < 0.05$) pairwise comparisons using Bonferroni's correction are displayed as †, ‡ or §, where the value is significantly different from respective named columns. HFA-BDP 100, HFA-BDP at 100 μg/day; HFA-BDP400, HFA-BDP at 400 μg/day.

Variable	Baseline HFA-BDP100†	HFA-BDP400 + placebo‡	HFA-BDP100 + propranolol§	P value (ANOVA)
Histamine PC ₂₀ (mg/ml)*	1.31 (0.66, 2.63)	2.71 (1.87, 3.95)†§	1.48 (1.00, 2.19)	0.007
F _E NO (ppb)*	29 (21, 41)	19 (15, 25)†	25 (18, 35)	0.01
Eosinophils ($\times 10^9$ /l)	0.29 (0.22, 0.35)	0.19 (0.16, 0.22)†§	0.31 (0.24, 0.39)	0.001
ECP (μg/l)*	22.3 (15.8, 31.4)	15.3 (10.5, 22.4)§	23.3 (17.1, 31.8)	0.006
OUCC (nmol/mmol)*	5.14 (3.92, 6.75)	3.85 (2.71, 5.46)	3.73 (2.65, 5.27)	0.22
FEV ₁ (% predicted)	91.6 (86.6, 96.7)	91.4 (87.1, 95.6)	88.9 (84.9, 92.9)	0.21
FEF ₂₅₋₇₅ (% predicted)	60.3 (50.6, 69.9)	58.8 (50.3, 67.3)	54.6 (47.6, 61.7)	0.055
R5 (% predicted)*	135 (111, 165)	144 (123, 169)	152 (130, 178)	0.22
R5–R20 (kPa/litres per s)*	0.06 (0.03, 0.12)	0.08 (0.05, 0.13)	0.10 (0.06, 0.16)	0.21
ACQ score	0.57 (0.30, 0.84)	0.49 (0.29, 0.69)	0.65 (0.36, 0.94)	0.41
AQLQ symptoms	6.19 (5.87, 6.51)	6.51 (6.30, 6.72)†§	6.21 (5.89, 6.54)	0.004
AQLQ overall	6.16 (5.88, 6.44)	6.41 (6.15, 6.67)	6.20 (5.92, 6.49)	0.053
Supine HR (bpm)	75.3 (70.5, 80.0)	76.1 (71.7, 80.5)	65.7 (62.2, 69.3)††	<0.001
Supine systolic BP (mmHg)	127 (119, 135)	127 (118, 135)	119 (112, 126)††	0.01
Supine diastolic BP (mmHg)	79 (73, 85)	79 (73, 85)	71 (66, 77)††	<0.001

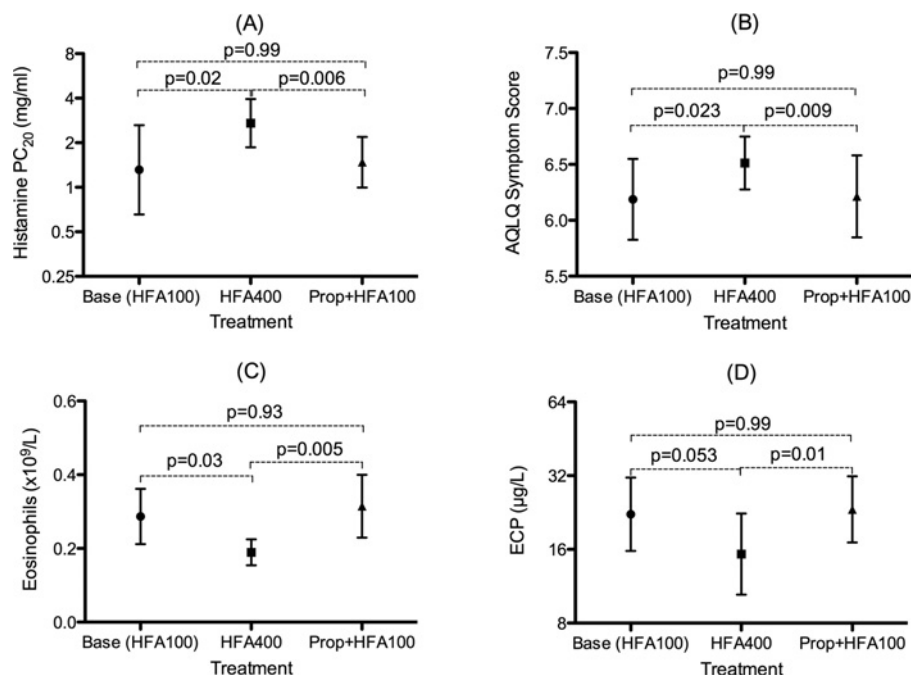


Figure 3 AHR, symptoms, blood eosinophils and serum ECP

Data are presented as arithmetic means (unless stated) with 95% CI error bars for baseline on HFA-BDP at 100 µg/day (HFA100) (circle), HFA-BDP at 400 µg/day plus placebo (HFA400) (square) and propranolol at 80 mg/day plus HFA-BDP at 100 µg/day (Prop + HFA100) (triangle). **(A)** Histamine PC₂₀ (primary outcome). Geometric means (95% CI). **(B)** AQLQ symptom component. **(C)** Blood eosinophils. **(D)** Serum ECP. Geometric means (95% CI).

Table 3 Salbutamol recovery outcomes post-histamine challenge

FEV₁ and ipratropium bromide (IB) data are following recovery to within 5% of baseline FEV₁ monitored at 5 min intervals. HR, BP and potassium were measured at 15 min post-nebulized salbutamol at 5 mg. All data are presented as means (95% CI) unless otherwise stated. *Median (interquartile range). **Absolute number of cases. Overall significance with repeated-measures ANOVA unless otherwise stated. Significant ($P < 0.05$) pairwise comparisons using Bonferroni's correction are displayed as † or ‡, where the value is significantly different from respective named columns. §Related samples Friedman's two-way ANOVA. ††Related samples Cochran's Q test. HFA-BDP100, HFA-BDP at 100 µg/day; HFA-BDP400, HFA-BDP at 400 µg/day.

Variable	Baseline HFA-BDP100†	HFA-BDP400+placebo‡	HFA-BDP100+propranolol	P-value (ANOVA)
FEV ₁ (% predicted)	92.8 (88.4, 97.1)	91.7 (87.9, 95.5)	86.4 (82.3, 90.4)†‡	0.001
Time to >95% base FEV ₁ (min)*	5 (5, 5)	5 (5, 10)	12.5 (5, 15)	0.002§
IB given at 15 min (n)**	0	0	3	0.05††
Supine HR (bpm)	93.3 (87.0, 99.5)	96.0 (92.1, 99.9)	65 (60, 71)†‡	<0.001
Supine systolic BP (mmHg)	135 (128, 143)	136 (129, 143)	122 (114, 129)†‡	<0.001
Potassium (mmol/l)	3.6 (3.4, 3.8)	3.6 (3.4, 3.8)	4.3 (4.1, 4.4)†‡	<0.001

score compared with both baseline and propranolol but less than the minimal important difference of 0.5 (Table 2, Figure 3B).

Airway calibre

There was a significant reduction in domiciliary evening FEV₁ with propranolol compared with both baseline and placebo [mean 0.22 litres (95% CI: 0.10–0.34) from baseline; $P = 0.012$]. This was only evident with the highest propranolol dose (80 mg/day) and not with 40 mg/day during week 2 of up-titration (Table 4). There was no significant fall in domiciliary morning FEV₁ with either propranolol dose (Table 4). Visit-based spirometry and IOS measures, including total airway resistance at 5 Hz (R5), did not significantly change with either randomized treatment compared with baseline (Table 2).

Adrenal function

We have found no significant systemic suppression of adrenal function, using OUCC, with either treatment compared with baseline (Table 2).

DISCUSSION

The results of the present study demonstrated that adding propranolol to low-dose ICS in persistent asthma did not significantly change histamine AHR, whereas increasing the dose of ICS conferred a significant further improvement. In other words, propranolol did not demonstrate any corticosteroid-sparing effect on AHR, a hallmark of the underlying asthmatic disease process. Moreover, we have found significant room for further

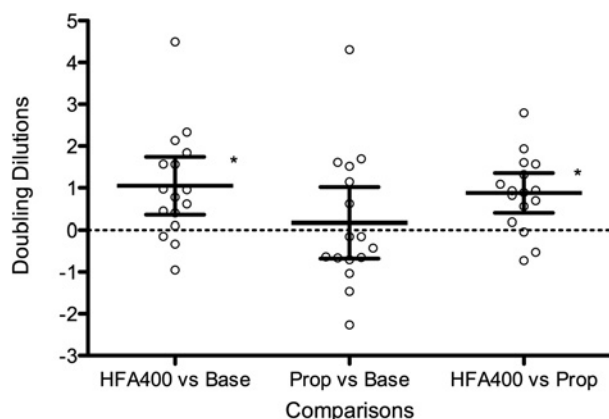


Figure 4 Histamine PC₂₀ dd differences

Scatter plots of individual histamine dd differences between all comparisons of baseline and both treatments with means and 95% CI error bars. Horizontal interrupted line indicates unity. * $P < 0.05$ between treatments. Base, baseline measurements post-run-in on HFA-BDP at 100 $\mu\text{g/day}$; HFA400, HFA-BDP at 400 $\mu\text{g/day}$ plus placebo; Prop, propranolol plus HFA-BDP at 100 $\mu\text{g/day}$.

improvement with the higher ICS dose for local and systemic inflammatory outcomes, namely F_{ENO} , blood eosinophils and serum ECP, whereas adding propranolol to low-dose ICS did not significantly affect these.

The novel counterintuitive theory that β -blockade might be effective in the treatment of asthma came through β -adrenoceptor basic science and murine models of asthma. Inverse agonist activity occurs at the B2ADR in the presence of certain β -blockers, including propranolol and nadolol, essentially 'switching off' the

receptor by reducing basal constitutional activity [18,19] with the potential, therefore, to up-regulate other B2ADRs. However, other data would tend to negate the role of inverse agonism, whereby adrenaline (epinephrine) depletion in the mouse model resulted in inhibition of allergen-induced asthma [20]. Other theories have postulated that certain β -blockers such as nadolol and timolol might confer anti-asthmatic properties unrelated to their inverse agonism, such as inhibition of pro-inflammatory signalling pathways involving β -arrestin and ERK (extracellular-signal-regulated kinase) [19,21]. However, the putative role of such *in vitro* anti-inflammatory activity in humans with asthma remains to be proven in placebo-controlled trials.

Open-label studies in mild steroid-naïve asthmatic patients showed that nadolol resulted in a 4.7% fall in pre-challenge FEV_1 , with a preserved bronchodilator response to high-dose salbutamol post-challenge [7,8]. This preserved salbutamol response might be explained by previous data from human peripheral blood lymphocytes, which have shown that marked B2ADR up-regulation occurs within 2 days of chronic exposure to propranolol, with a fully restored isoproterenol-induced cAMP response after 2 weeks [22]. In our previous study [12] and in the present report, we have shown partial blunting of salbutamol recovery post-challenge with propranolol compared with placebo. Pointedly, the partially preserved bronchodilator response to salbutamol post-challenge in the presence of propranolol occurred despite complete attenuation of systemic B2ADRs in the form of salbutamol-induced hypokalaemic and chronotropic responses, in turn suggesting much higher local than systemic receptor occupancy by inhaled salbutamol. Presumably, it might be possible to completely overcome airway B2ADR occupancy by

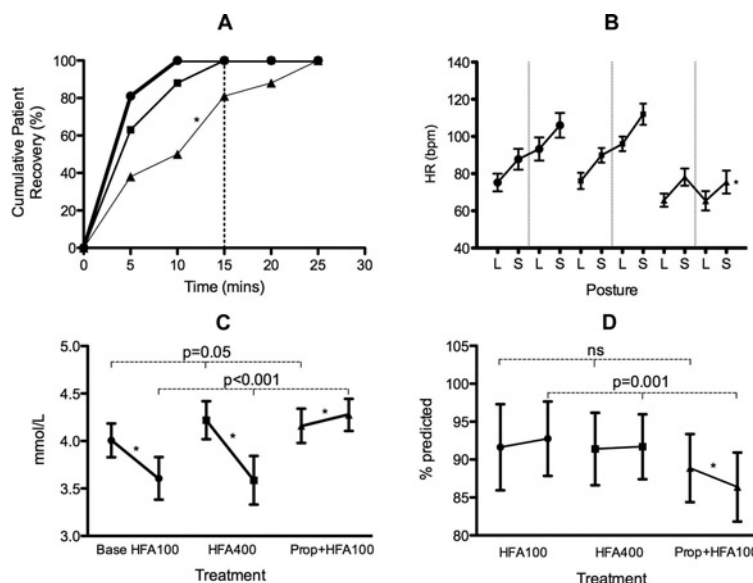


Figure 5 FEV₁ recovery post-salbutamol, and HR, serum potassium and FEV₁ pre- and post-salbutamol

Values are arithmetic means (unless stated) with 95% CI: baseline HFA-BDP at 100 $\mu\text{g/day}$ (HFA100) (circle), HFA-BDP at 400 $\mu\text{g/day}$ plus placebo (HFA400) (square) and propranolol at 80 mg/day plus HFA-BDP at 100 $\mu\text{g/day}$ (Prop + HFA100) (triangle). (A) Cumulative recovered patients $>95\%$ baseline FEV_1 . Data: absolute values. Vertical line: ipratropium administration. * $P = 0.02$ propranolol compared with baseline/placebo. (B) HR. L/S = lying/standing. Vertical lines: pre-/post-challenge. * $P < 0.001$ propranolol compared with baseline/placebo. (C) Potassium. Lines join pre-/post-challenge (* $P < 0.05$). (D) FEV_1 . Lines join pre-/post-challenge (* $P < 0.05$).

Table 4 Domiciliary FEV₁ at mid-point and end of treatments

Domiciliary data are presented as 7-day rolling means (95% CI) over week 2 of run-in as well as week 2 (propranolol 40 mg/day or placebo) and week 4 (propranolol 80 mg/day or placebo) of both treatment periods. Overall significance with repeated-measures ANOVA. Significant ($P < 0.05$) pairwise comparisons using Bonferroni's correction are displayed as *, † or ‡, where the value is significantly different from respective named columns. HFA-BDP100, HFA-BDP at 100 µg/day; HFA-BDP400, HFA-BDP at 400 µg/day.

Variable	Baseline HFA-BDP100*	HFA-BDP at 400 + placebo†	HFA-BDP 100 + propranolol‡	P value (ANOVA)
Propranolol at 40 mg				
Morning FEV ₁ (litres)	2.96 (2.60, 3.33)	2.99 (2.67, 3.30)	2.91 (2.58, 3.24)	0.32
Evening FEV ₁ (litres)	2.98 (2.62, 3.34)	2.95 (2.65, 3.26)	2.90 (2.57, 3.22)	0.19
Propranolol at 80 mg				
Morning FEV ₁ (litres)	2.96 (2.60, 3.33)	2.95 (2.65, 3.26)	2.84 (2.53, 3.15)	0.08
Evening FEV ₁ (litres)	2.98 (2.62, 3.34)	2.92 (2.60, 3.24)	2.76 (2.46, 3.06) ^{††}	0.002

propranolol if one was to give much higher nebulized doses of salbutamol than the 5 mg used in the present study. We were cautious about doing this because of the possibility of causing greater B2ADR-mediated systemic adverse effects in the placebo arm.

Studies have consistently shown a dose response to ICS for AHR in asthma [23]. This was integral to the present study design by including a positive control arm with high-dose ICS, both to demonstrate any room for further improvement over low-dose ICS and, therefore, any putative steroid-sparing effect of propranolol on AHR and to confirm that we had adequate power to detect any clinically important change in the primary outcome of histamine AHR. It is clear, therefore, from the present study that there is no effect of chronic propranolol on AHR in persistent asthma as the histamine PC₂₀ values were similar both pre- and post-propranolol, while taking the same 100 µg dose of HFA-BDP. This adds to our previous data, where we have found no additional effect of chronic propranolol over and above medium-dose ICS at a BDP equivalent dose of 440 µg/day [12], by answering the question of whether there might have been no additional room for improvement in AHR at this dose.

Dose-dependent ICS effects have also been demonstrated on other inflammatory outcomes. There is a significant dose response of F_ENO with incremental ICS [24,25], albeit most improvement occurs with low-dose ICS. Nevertheless, we did demonstrate significant improvements in F_ENO, blood eosinophilia and serum ECP with the increased dose of ICS but not with propranolol, suggesting there is no additional anti-inflammatory effect with chronic β-blockade in the presence of low-dose ICS. Furthermore, given that we have found no difference between randomized treatments in regard to urinary cortisol levels, these effects on systemic allergic biomarkers (eosinophils and ECP) are more likely to be due to topical effects on the airway of higher dose HFA-BDP rather than any increased systemic activity.

We believe it noteworthy that chronic propranolol did not result in any significant worsening of AHR, F_ENO, eosinophils, ECP, symptoms (AQLQ) or overall asthma control (ACQ), with only a minor reduction in domiciliary evening FEV₁. Indeed, this was with a usual 80-mg dose of sustained-release propranolol sufficient to cause a 10-bpm mean reduction in supine HR as well as a significant reduction in resting BP.

On the basis of the screening FEV₁ (mean 86.4%), ICS dose (406 µg/day), AHR (mean PC₂₀ 1.39 mg/ml) and F_ENO levels

[mean 40 parts per billion (ppb)], our cohort would be classified as having persistent asthma; one would, therefore, have expected them to fare worse when given propranolol especially while only taking low-dose ICS. This preservation of outcomes on propranolol may perhaps be due to using a gradual dose ramp [7] of propranolol over several weeks, as well as co-prescribing the long-acting muscarinic antagonist tiotropium in order to avert any potential catastrophic fall in FEV₁ upon first exposure to β-blockade [15]. However, it may also simply be that the presence of ICS even at low dose is intrinsically bronchoprotective against propranolol.

In keeping with previous studies that found significant reductions in FEV₁ (approximately 5%) with chronic β-blockade [7,11], we have also demonstrated a significant reduction in evening domiciliary FEV₁ with propranolol amounting to 0.22 litres (i.e. a 7.4% fall). Furthermore, we did not demonstrate any significant improvement with high-dose ICS on airway calibre measurements, presumably because these were relatively preserved at baseline. There was a small improvement in the AQLQ symptom score with high-dose ICS, but this was less than the minimum important difference of 0.5 [26]. Moreover, there was no change in ACQ throughout the study, with mean scores indicating well-controlled asthma from the outset.

We believe that the strengths of the present study are in its prospective randomized placebo-controlled design, particularly with regard to including a positive control arm (high-dose ICS), which proved effective in demonstrating potential room for further improvement in the primary outcome measure of histamine AHR. Furthermore, we have shown that the present study design has robust safety attributes in using a gradual dose ramp for propranolol and in providing protection with concomitant long-acting muscarinic antagonist therapy during this up-titration period.

One of the main limitations of the present study may also be related to our focus on safety as evidenced by initial clinical stability (as seen by the ACQ score) and relatively well-preserved pulmonary function on study entry, thus leaving relatively little room for improvement in these outcomes upon chronic propranolol exposure. Another limitation may be due to small patient numbers, although the present study was powered on the primary outcome of histamine AHR in terms of being able to detect a difference of 1 dd.

Conclusions

Adding propranolol to low-dose ICS in persistent asthma provides no corticosteroid-sparing effect on histamine AHR and other inflammatory outcomes compared with the significant improvements conferred by using a higher ICS dose. Salbutamol recovery post-histamine challenge was blunted partially, and there was a small but significant fall in evening FEV₁ when adding propranolol to low-dose ICS, but no deterioration in ACQ or AQLQ. We would not, therefore, advocate propranolol as a corticosteroid-sparing agent in persistent asthma. However, clinical equipoise might still be challenged as propranolol could perhaps be given at these doses to asthmatic patients for its usual indications, provided our strict safety criteria are adhered to in carefully selected patients controlled on ICS.

CLINICAL PERSPECTIVES

- In the murine asthma model, switching off β_2 receptors with an inverse agonist confers corticosteroid-sparing acting activity. We have, therefore, investigated whether this effect occurred in patients with asthma by adding the inverse agonist propranolol to a low dose of ICS compared with a higher dose of ICS alone.
- We have shown that increasing the ICS dose conferred significant improvements in histamine-induced AHR (the primary outcome), inflammatory markers and symptoms, whereas no such effects occurred when propranolol was added to low-dose ICS.
- Thus, we have found no evidence to support a clinically meaningful ICS-sparing effect conferred by propranolol in asthma.

AUTHOR CONTRIBUTION

Brian Lipworth, Peter Williamson and William Anderson are responsible for the study conception and design. William Anderson, Philip Short, Peter Williamson and Arvind Manoharan are responsible for the acquisition of data. William Anderson and Brian Lipworth are responsible for the analysis and interpretation of data. William Anderson, Philip Short, Peter Williamson, Arvind Manoharan and Brian Lipworth are responsible for drafting the article or revising critically for important intellectual content. All the authors approved the final version to be published. William Anderson and Brian Lipworth had full access to all of the data in the study. Brian Lipworth is the guarantor for the content of the manuscript, the integrity of the data and the accuracy of the data analysis

ACKNOWLEDGEMENTS

We thank the TEVA Pharmaceuticals for their educational gift of HFA-BDP inhalers, and Boehringer Ingelheim for their educational gift of tiotropium inhalers for the study. We also thank the St. Mary's Pharmaceutical Unit, Cardiff, U.K., and the Vale University Local Health Board, Cardiff, Wales, U.K., for their support in investigational medicinal product manufacture, and the Immunoassay

Biomarker Core Laboratory, Medical Research Institute, University of Dundee for biochemical assays

FUNDING

The present study was funded by the Chief Scientist Office Scotland [grant number CZB/4/716]. The sponsor had no role in the present study other than financial support.

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Received 22 April 2014/27 May 2014; accepted 18 June 2014

Published as Immediate Publication 18 June 2014, doi: 10.1042/CS20140249