Effects of hydrocortisone on acute β -adrenoceptor blocker and histamine induced bronchoconstriction

Philip M. Short, Peter A. Williamson & Brian J. Lipworth

Asthma and Allergy Research Group, Centre for Cardiovascular and Lung Biology, Division of Medical Sciences, University of Dundee, Dundee, UK

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- β -adrenoceptor blockers are avoided in asthma due to concerns of the potential for β -adrenoceptor blocker induced bronchoconstriction with the greatest risk after first dose.

WHAT THIS STUDY ADDS

- Nebulized salbutamol and ipratropium produced a full recovery of lung function in the presence of acute β -adrenoceptor blocker and histamine induced bronchoconstriction. Salbutamol reversibility was not potentiated by intravenous hydrocortisone.

Correspondence

Professor Brian J. Lipworth MD, Asthma and Allergy Research Group, Centre for Cardiovascular and Lung Biology, Division of Medical Sciences, University of Dundee, Dundee DD1 9SY, UK.

Tel.: +44 13 8263 2983 (direct)

+44 13 8263 2180 (secretary)

Fax: +44 13 8264 4972

E-mail: brianlipworth@gmail.com

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AIMS

β -adrenoceptor blockers are avoided in asthma due to concerns of bronchoconstriction. We investigated the safety of acute exposure to propranolol in asthmatics, sequentially challenged with histamine to mimic an asthma exacerbation and evaluated the role of intravenous hydrocortisone in potentiating salbutamol reversibility.

METHODS

Persistent atopic asthmatics, requiring $\leq 1000 \mu\text{g day}^{-1}$ budesonide, performed a randomized double-blind placebo-controlled crossover study. Following 10 mg or 20 mg of oral propranolol, patients received 400 mg intravenous hydrocortisone or placebo, followed by histamine challenge with nebulized salbutamol 5 mg and ipratropium 500 μg recovery.

RESULTS

Thirteen patients completed per protocol. Hydrocortisone did not potentiate salbutamol recovery post propranolol and histamine challenge vs. placebo (mean difference in FEV_1 0.04 ml, 95% CI -0.07, 0.15, $P = 0.417$). β -adrenoceptor blocker induced bronchoconstriction was demonstrated by spirometry and impulse oscillometry. For the placebo visit, FEV_1 fell 4.7% 2 hours post propranolol (95% CI 1.8, 7.5, $P = 0.008$) whilst total airway resistance ($R5\%$) increased 31.3% (95% CI 15.6, 47.0, $P = 0.04$). On both visits $\text{FEV}_1\%$ and $R5\%$ returned to baseline after salbutamol post histamine.

CONCLUSION

Nebulized salbutamol and ipratropium produced a full recovery after propranolol and histamine induced bronchoconstriction, independent of hydrocortisone use. Since the greatest risk of β -adrenoceptor blockade is after first dose, our findings offer reassurance to those undertaking further evaluation of chronic β -adrenoceptor blockade as a potential treatment for mild-to-moderate asthma.

Introduction

In 1964 propranolol, a non-selective β -adrenoceptor blocker was released following its discovery by the late Nobel Laureate Sir James Black [1]. Although β -adrenoceptor blockers revolutionized the treatment of cardiovascular disease, there were concerns of their use in asthmatics due to risk of bronchospasm.

β -adrenoceptor blocker induced bronchoconstriction is most pronounced following the first dose with non-selective drugs due to β_2 -adrenoceptor antagonism. First shown by McNeill, in a group of 10 asthmatic patients, the mean fall in FEV₁ was 23% (range 6–56%) following 5–10 mg of intravenous propranolol [2].

Concern regarding β -adrenoceptor blocker use in asthma increased throughout the 1980s with case reports and guidance stating that β -adrenoceptor blockers, regardless of selectivity, should not be used in asthmatics due to risk of bronchospasm [3–5]. However when applied to larger asthmatic study populations, co-prescription of β -adrenoceptor blockers and β -adrenoceptor agonists has been reported [6, 7].

A meta-analysis has examined cardioselective β -adrenoceptor blocker use in reactive airways disease. Although FEV₁ mean fall was 7.5% following single dosing, no significant fall was seen with chronic dosing [8]. This disconnect between acute and chronic effects mirrors the response seen to β -adrenoceptor blocker use in heart failure. Once contraindicated due to concerns following acute dosing, β -adrenoceptor blockers are now established as a main chronic treatment choice for heart failure [9].

With these reassurances, studies have begun to explore the potential therapeutic benefits of chronic β -adrenoceptor blockade in asthma. The non-selective β -adrenoceptor blocker, nadolol has been shown to reduce airway hyper-responsiveness (AHR) and inflammation and may lead to up-regulation of β_2 -adrenoceptors in murine models [10–12]. This led to two open pilot studies in steroid naïve asthmatics, with chronic nadolol dosing achieving significant improvements in AHR [13, 14].

Patients' safety is paramount when conducting clinical trials with non-selective β -adrenoceptor blockers in asthma [15]. Although salbutamol reversibility has been shown to be preserved following chronic β -adrenoceptor blockade with the non-selective β -adrenoceptor blocker nadolol [14], concerns remain during the early period of β -adrenoceptor blocker exposure, primarily following the first dose, before any disease modifying activity has occurred.

Previous studies have identified it takes approximately 2 weeks for β_2 -adrenoceptor up-regulation to occur, suggesting this would be the theoretical at risk period during up-titration with β -adrenoceptor blockade in asthmatics [16, 17].

We wished to establish whether ingestion of a single dose of oral propranolol would prevent subsequent salb-

utamol and ipratropium recovery, following histamine challenge to mimic acute bronchoconstriction present during an asthma exacerbation.

Importantly we wished to know if acute administration of intravenous hydrocortisone might partially obviate the effects of acute β_2 -adrenoceptor blockade and improve the effects of nebulized salbutamol due its acute facilitatory effects on β_2 -adrenoceptors within 3 h of administration [18].

Methods

Study subjects

Persistent atopic asthmatics, FEV₁ > 80% predicted, taking ≤ 1000 μ g budesonide or equivalent (BDP) of inhaled corticosteroids (ICS), aged 18–65 years and who had AHR to histamine challenge, were recruited. All participants were non-smokers. Exclusions included resting systolic blood pressure (BP) < 100 mmHg and heart rate (HR) < 60 beats min⁻¹, history of arrhythmias, diabetes or rate limiting medications. Subjects were invited to participate from a list of known volunteers who had expressed an interest to take part in clinical trials within our department. Potential participants received a written participant information sheet detailing the trial requirements and the extent of their participation before attending for a screening visit. Informed written consent was obtained following discussion with a respiratory physician.

Study design

A double-blind randomized placebo controlled crossover study was performed, consisting of an average of three (maximum four) separate laboratory study visits over 3 weeks (Figure 1). The Tayside Medical Research Ethics Committee gave approval before commencement of the trial. The study was registered with <http://www.clinicaltrials.gov> (NCT 01070225). Blinding and randomization of treatment limbs were performed by the Clinical Trials Pharmacist, University of Dundee.

At screening, spirometry, impulse oscillometry (IOS), histamine bronchial challenge (PC10) and skin prick testing were performed. Participants were issued a peak expiratory flow meter (PEF) meter and continued on their regular ICS dose. Long acting β -adrenoceptor agonist (LABA) therapy was stopped during the study. Combination ICS/LABA was switched to ICS alone.

At the 1 week post screening visit, participants underwent their first 6 h laboratory study visit. Following baseline spirometry and IOS, domiciliary PEF was analyzed to ensure <20% diurnal variation. Participants ingested a 10 mg propranolol tablet. Spirometry, IOS, BP and HR were observed. At 2 h, if the fall FEV₁ $\geq 10\%$ the study visit continued. If FEV₁ fell <10%, the study visit ended and was repeated on a separate day using 20 mg propranolol.

Figure 1

Study visit diagram. Hist histamine, salb salbutamol, IP ipratropium

Participants were randomized to receive 400 mg of intravenous hydrocortisone or placebo (0.9% NaCl) 2 h post propranolol (10 mg or when required 20 mg).

At 4 h post propranolol, participants underwent histamine challenge (PC10) with reversibility to sequential salbutamol 5 mg and ipratropium 500 µg nebulizers. Spirometry and IOS were performed 20 min post salbutamol and ipratropium. Serum potassium was measured at baseline, 2 and 4 h post propranolol and 20 min post salbutamol. A final study visit was performed where treatment limbs were crossed over (duration between visits 3–5 days). The participant received either intravenous hydrocortisone or placebo (0.9% NaCl) depending on their initial randomization. At all study visits, the investigator was blinded to the treatment given (hydrocortisone or placebo). The same dose of propranolol was used and the visit was repeated as outlined above.

Measurements

Spirometry was performed in accordance with published guidelines [19]. IOS was also performed as an alternative measure of assessing lung function. IOS is an effort independent method of assessing airway resistance by the use of small amplitude sound waves being superimposed on normal breathing cycles and was performed in accordance with published guidelines [20]. A SuperSpiro spirometer (Micro Medical, UK) and IOS Jaeger Masterscreen (Germany) were used. Histamine bronchial challenge (PC10) was performed using a Mefar dosimeter with doubling concentrations from 0.312–540 mg ml⁻¹. The provocative concentration of histamine required to cause a 10%, and not the standard 20% fall in FEV₁, was calculated (PC10) in view of safety. We did not use methacholine challenge as this would be directly antagonized by ipratropium. Skin prick testing with eight common aeroallergens (Merck, United Kingdom) was performed. For the purpose of this study, atopy was defined as having one or more positive skin prick tests to common allergens (grasses, trees, weeds, house dust mites, aspergillus, feathers, dog and cat).

Analysis

Data were analyzed for normality with Shapiro-Wilk tests and Boxplots. The primary analysis was the difference in salbutamol recovery for hydrocortisone vs. placebo. Recovery was determined as change in FEV₁ (ml) post salbutamol from lowest post histamine FEV₁. *A priori* calculation predicted 13 patients would have an 80% power to detect a difference of 200 ml between recovery FEV₁ with a two-sided significance level of 0.05, assuming a within-patient standard deviation of 150 ml. Salbutamol recovery was also assessed by change in FEV₁ % predicted and R5% predicted. Secondary analysis included assessment of β -adrenoceptor blocker induced bronchoconstriction, the effects of β -adrenoceptor blockade on staged salbutamol and ipratropium reversibility post histamine challenge and evidence of systemic β -adrenoceptor blockade (serum potassium, HR, BP). Analysis of variance of repeated measures was performed with Bonferroni correction for pairwise comparisons with a two-tailed α -error set at 0.05. All analyses were performed on a per protocol basis using SPSS version 17 (SPSS Inc, Chicago, IL).

Results

Demographics

Of 26 participants screened, 15 were randomized. A total of 13 participants (seven male, six female) completed the study (Figure 2). Mean age (SEM) was 34 (3). Two participants withdrew as they could not complete the study visits for personal reasons. Eleven participants had less than a 10% fall in FEV₁ after 10 mg propranolol and subsequently were given 20 mg. There were no adverse events following β -adrenoceptor blocker ingestion, (for demographics see Table 1).

Comparison between study visits

There were no significant differences between the histamine PC10 (mg ml⁻¹) on study visits (hydrocortisone and placebo) and the screening visit.

Figure 2
Consort diagram

Primary analysis

Effect of hydrocortisone on nebulized salbutamol post sequential β -adrenoceptor blockade and histamine challenge There was no significance difference in salbutamol recovery measured by change in FEV₁ post histamine challenge following intravenous hydrocortisone vs. placebo (mean difference 0.04 ml, 95% CI -0.07 , 0.15 , $P = 0.417$). There was also no change when comparing FEV₁ % predicted (mean difference 6.6, 95% CI -5.9 , 19.1 , $P = 0.263$), R5 (mean difference 0.03 kPa l⁻¹ s, 95% CI -0.03 , 0.08 , $P = 0.274$) and R5 % predicted (mean difference 10.9, 95% CI -9.0 , 30.9 , $P = 0.255$). Therefore intravenous hydrocortisone did not potentiate the effect of salbutamol recovery post sequential β -adrenoceptor blockade and histamine challenge.

Secondary analyses

Analysis of β -adrenoceptor blocker induced bronchoconstriction For the hydrocortisone visit there was a fall in FEV₁ % predicted 2 h post propranolol of 3.8% (95% CI -0.9 , 8.5 , $P = 0.083$), whilst at the placebo visit a significant fall of 4.7% was observed (95% CI 1.8 , 7.5 , $P = 0.008$). No significant falls in FEV₁% were observed at 4 h post propranolol on either visit (Table 2, Figure 3). There was a significant increase in R5 % predicted at 2 and 4 h post propranolol on both visits, with a mean increase of 31.3% on the placebo visit at 2 h (95% CI 15.6 , 47.0 , $P = 0.04$) (Table 2, Figure 3). R5 and R5–20 showed significant increases at both 2 and 4 h post propranolol (see Table 3).

Systemic β_1 - and β_2 -adrenoceptor blockade Heart rate was significantly lower 2 h post propranolol at the hydro-

cortisone (mean change 20 beats min⁻¹, 95% CI 14 , 27 , $P < 0.001$) and placebo visits (mean change 16 beats min⁻¹, 95%CI 13 , 20 , $P < 0.001$). No significant changes were observed with blood pressure post propranolol ingestion. Serum potassium concentrations were significantly increased at 4 h post propranolol on both visits, and did not reverse back to baseline following salbutamol recovery (Figure 3), thus showing evidence of sustained β_2 -adrenoceptor blockade throughout the study.

Reversibility post sequential β -adrenoceptor blockade and histamine challenge On both visits all spirometry (FEV₁, FVC) and IOS measurements (R5, R20, R5–R20, X5) either returned back to baseline values or significantly improved in comparison with baseline after nebulized salbutamol, with only small further improvements seen following ipratropium (Figure 3, Tables 2–4).

Discussion

The major issue when conducting clinical trials using β -adrenoceptor blockers in asthma is patient safety. Whilst salbutamol has been shown to reverse bronchial challenge induced bronchoconstriction following chronic β -adrenoceptor blockade, this has not been reported following acute β -adrenoceptor blockade [14]. We have demonstrated that nebulized salbutamol is able to reverse sequential single dose propranolol and histamine induced bronchoconstriction in our study population.

Our primary study endpoint was to assess if acute administration of intravenous hydrocortisone might partially obviate the effects of acute β_2 -adrenoceptor blockade and improve the effects of nebulized salbutamol. Subsensitization of β_2 -adrenoceptors occurs following treatment with LABAs [21, 22]. Previous work in our department has shown that high dose systemic corticosteroids (200 mg intravenous hydrocortisone with 50 mg oral prednisolone) can re-establish the β_2 -adrenoceptor function following agonist promoted down-regulation [18]. These effects were seen in patients already taking inhaled corticosteroids with a median dose of 1000 μ g day⁻¹ budesonide, thus suggesting that systemic corticosteroids have a dual action in acute asthma, with effects on the β_2 -adrenoceptor response as well as an established anti-inflammatory response. It therefore seemed plausible in this instance that a similar response may occur with intravenous corticosteroid following acute β -adrenoceptor blockade (i.e. reversal of β -adrenoceptor blockade whilst re-establishing β -adrenoceptor agonist sensitivity).

Our study showed that intravenous hydrocortisone did not potentiate the effect of salbutamol on FEV₁ recovery post sequential β -adrenoceptor blockade and histamine challenge. It is worth pointing out though, that even in the placebo arm salbutamol reversed histamine induced bronchoconstriction back to baseline. Therefore there may have

Table 1

Demographics

Subject/ Gender	Age (years)	FEV ₁ %	R5 %	Histamine PC10 (mg ml ⁻¹)	BDP equivalent daily dose (μ g)	Duration of asthma symptoms (years)
1/F	20	100	174	0.44	400	10
2/F	40	106	136	8.41	800	6
3/F	42	106	81	7.07	800	15
4/F	19	96	127	0.14	400	12
5/F	44	104	160	1.98	800	30
6/F	23	118	97	8.91	1000	10
7/M	24	86	160	2.18	400	15
8/M	44	92	112	1.89	1000	20
9/M	30	92	89	1.77	400	24
10/M	63	92	114	0.71	200	50
11/M	30	97	153	10.59	800	18
12/M	26	90	183	0.35	400	6
13/M	34	92	169	0.28	800	5
Mean (SEM)	34 (3)	98 (2)	135 (9)	3.44 (1.1)	631 (75)	17 (3)

Data shown as % predicted for age, gender, race. FEV₁ forced expiratory volume in 1 s, R5 resistance at 5 Hz, PC10 provocative concentration required to achieve 10% fall in FEV₁, BDP budesonide.

Table 2FEV₁ % and R5 % throughout study visits

Outcome	I.v. hydrocortisone visit (Mean, SEM)	Placebo (i.v. 0.9% NaCl) visit (Mean, SEM)
FEV ₁ % predicted		
Baseline (t = 0 min)	95.4 (2.8)	97.4 (2.6)
2 h post propranolol (t = 120 min)	91.6 (3.2)	92.7 (2.9)*
2 h post i.v. hydrocortisone or saline (t = 240 min)	92.6 (2.8)	94.8 (2.9)
Post histamine challenge PC10 (t = 250 min)	78.0 (3.4)**	78.3 (3.9)**
20 min post salbutamol (t = 270 min)	99.2 (2.6)	100.3 (2.6)
20 min post ipratropium bromide (t = 290 min)	103.9 (2.8)*	104.4 (2.9)*
R5 % predicted		
Baseline (t = 0 min)	123.3 (10.5)	113.7 (6.3)
2 h post propranolol (t = 120 min)	149.0 (12.35)*	145.0 (11.4)*
2 h post i.v. hydrocortisone or saline (t = 240 min)	144.8 (10.36)*	136.8 (8.6)*
Post histamine challenge PC10 (t = 250 min)	183.3 (11.6)**	192.3 (16.9)**
20 min post salbutamol (t = 270 min)	99.6 (5.1)	97.7 (4.9)*
20 min post ipratropium bromide (t = 290 min)	98.1 (4.9)	90.6 (4.6)*

Data displayed as mean (SEM). *Significant difference between time point and baseline, $P < 0.05$. **Significant difference between time point and baseline, $P < 0.001$. Significance calculated by ANOVA of repeated measures with *post hoc* Bonferroni correction.

been no further room for improvement with intravenous corticosteroid. Moreover we ensured that LABAs were withdrawn for the duration of the study, such that there would have been no agonist promoted down-regulation, aside from the effects of on demand salbutamol in between study visits. However in a real life scenario of a patient having an asthma exacerbation whilst concurrently receiving β -adrenoceptor blockers, it would still be prudent to give acute systemic corticosteroids to treat any worsening airway inflammation, as well as reversing any down-regulation due to concomitant LABAs. Our study did not address the potential influence of acute corticosteroids on airway inflammation, because histamine works

directly on airway smooth muscle histamine receptors to produce bronchoconstriction.

We evaluated the relative sensitivity of spirometry and IOS at demonstrating the effects of β -adrenoceptor blocker induced bronchoconstriction. Due to safety concerns, and to mimic our proposed initial dose for a future chronic dosing study we used low doses of propranolol in this study. Despite our patients having relatively preserved spirometry, indicating mild-to-moderate disease, all our patients received inhaled corticosteroids for asthma control. In the selected cases where the baseline histamine PC10 was greater than 8 mg ml⁻¹, these patients all received at least 800 μ g day⁻¹ BDP. We can presume that

Figure 3

Effect of β -adenoreceptor blockade, bronchial challenge and sequential reversibility with salbutamol and ipratropium on separate study visits (hydrocortisone and placebo). FEV₁% (A and D), R5% (B and E) and serum potassium (D and F)

Figure 3

Continued

reducing inhaled corticosteroids would result in a worsening of response to histamine bronchial provocation. However the histamine PC10 threshold was irrelevant in this study, with the pertinent inclusion criteria being that each patient experienced a 10% fall in FEV₁ post histamine challenge, thus allowing us to assess reversibility to salbutamol and ipratropium in the presence of acute β -adrenoceptor blockade.

In view of the relatively preserved spirometry in our study subjects we used IOS to assess airway resistance. IOS has been shown to be a more sensitive marker of bronchodilation than spirometry in mild asthmatics receiving salbutamol, and thus we hypothesized IOS would be more sensitive at identifying any evidence of β -adrenoceptor blocker induced bronchoconstriction [23]. This proved to be the case with FEV₁ % predicted falling by 4.7% on the placebo visit at 2 h post propranolol with R5 % predicted (a measure of total airway resistance) increasing by 31.3% post propranolol at the same time point and visit. R5 % predicted also significantly increased by 25.7% on the hydrocortisone visit at 2 h post propranolol whilst FEV₁% did not fall significantly 2 h post propranolol. The difference in change in FEV₁ % predicted 2 h post propranolol between the hydrocortisone and placebo visit, highlights that in patients with preserved lung function, IOS is a more sensitive method of assessing bronchoconstriction and

the discordance in FEV₁ between visits may be partly due to daily FEV₁ variability. Furthermore airway resistance measured by R5, R20 and R5-R20 all showed persistent significant deterioration at 4 h post propranolol, whilst spirometry measures no longer demonstrated any evidence of bronchoconstriction at the same time point (prior to histamine challenge).

Heart rate and serum potassium measurements provided us with surrogate markers of systemic β_1 - and β_2 -adrenoceptor blockade respectively [24]. Serum potassium remained significantly elevated following ingestion of propranolol and failed reverse back to baseline following high dose salbutamol. This provides us evidence of sustained systemic β_2 -adrenoceptor blockade throughout the study period and supports previous work showing a prevention of salbutamol-induced hypokalaemia in the presence of propranolol 40 mg given as a single dose [25].

We have therefore demonstrated an unexpected disconnect between the interaction of propranolol and salbutamol on airway smooth muscle and skeletal muscle β_2 -adrenoceptors. Whilst the local concentration of salbutamol used in our study was clearly enough to overcome airway β_2 -adrenoceptor blockade conferred by propranolol, it was not enough to overcome antagonism of systemic skeletal muscle β_2 -adrenoceptors. Although we did not have a control arm where placebo propranolol was

Table 3
Impulse oscillometry (R5, R20, R5-20, X5) throughout study visits

Time point	Outcome R5 (kPa l ⁻¹ s)		R20 (kPa l ⁻¹ s)		R5-20		X5 (kPa l ⁻¹ s)	
	Hydrocortisone visit	Placebo visit	Hydrocortisone visit	Placebo visit	Hydrocortisone visit	Placebo visit	Hydrocortisone visit	Placebo visit
Baseline (t = 0 min)	0.363 (0.025)	0.341 (0.025)	0.313 (0.019)	0.316 (0.018)	0.050 (0.014)	0.025 (0.014)	-0.103 (0.014)	-0.098 (0.01)
2 h post propranolol (t = 120 min)	0.455 (0.039)**	0.440 (0.033)**	0.360 (0.020)*	0.351 (0.020)**	0.095 (0.024)*	0.089 (0.023)*	-0.143 (0.021)*	-0.139 (0.019)*
2 h post i.v hydrocortisone or saline (t = 240 min)	0.442 (0.033)**	0.416 (0.026)**	0.354 (0.021)	0.338 (0.015)*	0.088 (0.020)*	0.078 (0.019)**	-0.137 (0.019)	-0.127 (0.017)
Post histamine challenge PC10 (t = 250 min)	0.555 (0.033)***	0.580 (0.043)***	0.372 (0.018)*	0.360 (0.016)**	0.183 (0.028)***	0.219 (0.043)**	-0.211 (0.031)**	-0.216 (0.03)**
20 min post salbutamol (t = 270 min)	0.305 (0.019)	0.300 (0.019)	0.280 (0.018)	0.277 (0.015)**	0.025 (0.009)	0.023 (0.012)	-0.084 (0.01)	-0.085 (0.01)
20 min post ipratropium bromide (t = 290 min)	0.299 (0.017)	0.278 (0.017)*	0.275 (0.019)	0.261 (0.014)***	0.024 (0.008)	0.017 (0.012)	-0.082 (0.01)	-0.083 (0.01)

Data displayed as mean (SEM). *P < 0.05 compared with baseline, **P < 0.01 compared with baseline, ***P < 0.001 compared with baseline. Significance calculated by ANOVA of repeated measures with post hoc Bonferroni corrections.

given, we already know that 5 mg nebulized salbutamol on its own would be sufficient to induce significant hypokalaemia [26].

Heart rate showed a significant fall at 2 h post propranolol but this fall was not sustained at 4 h post propranolol, whilst markers of β_2 -adrenoceptor blockade persisted. Whilst peak blood concentrations following dosing with propranolol occur at approximately 2 h, with an elimination half-life of 4–6 h, this finding is unsurprising due to the relatively low dose of propranolol used and although non-selective, propranolol has a greater binding affinity to β_2 - than β_1 -adrenoceptors [27]. Indeed a similar finding has been reported with low dose nadolol in terms of preferential β_2/β_1 -adrenoceptor antagonism in man [24]. The β_2 -adrenoceptor binding affinity of propranolol is actually higher than that of nadolol, while its β_1 binding affinity is lower [27], thus making propranolol well suited for use in trials in asthma where a high degree of β_2 -adrenoceptor antagonism is required during the initial dose ramp. In this regard it has been shown that significant and near maximal up-regulation of peripheral blood lymphocyte β_2 -adrenoceptors occurs after 2 days of oral propranolol at 160 mg day⁻¹ in healthy volunteers [28].

Due to the known variability between subjects in the oral bioavailability of propranolol due to saturable first pass kinetics, we employed a step wise dose regime. Whilst our starting dose of 10 or 20 mg of propranolol is relatively low in comparison with the usual maintenance dose used in clinical practice for treatment of hypertension, angina and anxiety (usually 80–160 mg day⁻¹), we believe our study findings are clinically relevant since we were able to clearly demonstrate significantly sustained β_2 -adrenoceptor blockade. This was our first study using a contraindicated medication in asthma and thus we felt it was unethical to use a higher dose for initial exposure. However we have shown through the measurements of IOS and serum potassium evidence of sustained β_2 -adrenoceptor blockade at 4 h following 10 or 20 mg of propranolol. We accept our study was pilot in design and was small in sample size. However importantly we have observed no clinically relevant adverse effects with β -adrenoceptor blocker use in our study population. We deliberately chose well controlled asthmatics taking inhaled corticosteroids, and as such the first dose effects of propranolol were minimized. Thus the degree of bronchoconstriction seen in our study was less than seen by McNeill prior to the introduction of inhaled corticosteroids [2]. Our future trial will involve chronic dosing with propranolol as add on therapy to inhaled corticosteroids in well controlled mild-to-moderate asthmatics, and hence the present results are reassuring. Moreover as an extra precaution, we will be co-administering anticholinergic cover with tiotropium during the initial dose ramp with propranolol, since it has been shown that oxitropium prevents acute propranolol induced bronchoconstriction [29].

Table 4

Spirometry (FEV₁, FVC) throughout study visits

Time point	Outcome FEV ₁ (l)		FVC (l)	
	Hydrocortisone visit	Placebo visit	Hydrocortisone visit	Placebo visit
Baseline (t = 0 min)	3.23 (0.18)	3.30 (0.19)	4.19 (0.22)	4.20 (0.23)
2 h post propranolol (t = 120 min)	3.10 (0.18)	3.14 (0.18)*	4.00 (0.19)	4.05 (0.23)
2 h post i.v hydrocortisone or saline (t = 240 min)	3.14 (0.18)	3.20 (0.17)	4.02 (0.21)	4.10 (0.22)
Post histamine challenge PC10 (t = 250 min)	2.64 (0.16)***	2.62 (0.15)**	3.57 (0.22)**	3.60 (0.22)**
20 min post salbutamol (t = 270 min)	3.37 (0.19)	3.39 (0.17)	4.14 (0.22)	4.30 (0.18)
20 min post ipratropium bromide (t = 290 min)	3.51 (0.18)**	3.52 (0.18)**	4.24 (0.19)	4.27 (0.20)

Data displayed as mean (SEM). * $P < 0.05$ compared with baseline, ** $P < 0.01$ compared with baseline, *** $P < 0.001$ compared with baseline. Significance calculated by ANOVA of repeated measures with *post hoc* Bonferroni corrections.

In conclusion, we have demonstrated that a single low dose of oral propranolol caused a small but significant deterioration in airway calibre, which was more evident with IOS rather than spirometry. Importantly nebulized salbutamol and ipratropium produced a full recovery of FEV₁ and airway resistance after acute histamine induced bronchoconstriction in the presence of acute β -adrenoceptor blockade. Intravenous hydrocortisone did not potentiate salbutamol recovery post histamine challenge. However in a real-life scenario of an individual suffering an asthma exacerbation whilst receiving β -adrenoceptor blockers, intravenous corticosteroids remain vital due to their anti-inflammatory benefits. Since the greatest risk of β -adrenoceptor blockade is after first dose exposure with these reassurances we are now proceeding to evaluate effects of chronic dosing with propranolol as a potential treatment option for asthma.

Competing Interests

BJL has received grant support from Chief Scientist Office, Scotland to support research into beta-blockers in asthma including the salary for Dr.P.Short. There are no other competing interests to declare.

Contributions

All authors contributed to the study conception and design. PMS and BJL undertook the analysis and validation of the data. PMS wrote the first draft of the manuscript, with all authors contributing to the final draft. BJL is guarantor for the study.

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