

ORIGINAL ARTICLE

Effects of intravenous and oral β -blockade in persistent asthmatics controlled on inhaled corticosteroids

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ABSTRACT

Objective Despite their benefits in the treatment of cardiovascular disease, β -blockers are seldom used to treat asthmatics. We assessed the safety and tolerability of acute dosing with esmolol and propranolol in patients with asthma.

Design Post-hoc analysis of a double blind, randomised, placebo controlled trial of β -blocker use in asthma.

Patients Mild-to-moderate asthmatics on inhaled corticosteroids.

Interventions Each participant underwent a 6–8 week dose titration of oral propranolol. A subgroup received an intravenous bolus dose of esmolol (0.5 mg/kg). Measurements were recorded pre- and post-esmolol and first dose exposure to 10 mg, 20 mg, and 80 mg of propranolol. Tiotropium was given concurrently with propranolol. Bronchoconstriction was reflected as a fall in forced expiratory volume in 1 s (FEV₁) or increase in total airway resistance at 5 Hz (R5).

Results 12 patients completed the trial. There were no adverse effects on FEV₁% or R5% following intravenous esmolol. There were significant reductions at 2 min post-esmolol in heart rate (−4.7 beats/min (bpm), 95% CI −7.9 to −1.3 bpm; $p=0.002$) and systolic blood pressure (−5.9 mm Hg, 95% CI −11.4 to −0.4 mm Hg; $p=0.03$). No bronchoconstriction was seen during up titration following the first dose of 10 mg, 20 mg or 80 mg of propranolol in the presence of tiotropium. No difference in the asthma control questionnaire at 80 mg propranolol was seen versus placebo in the presence of tiotropium.

Conclusions Intravenous esmolol was administered without any adverse effects on pulmonary function in selected, stable, mild-to-moderate asthmatics controlled on inhaled corticosteroids. Tiotropium prevented propranolol induced bronchoconstriction after acute dosing during up-titration to 80 mg with no adverse impact on asthma control.

INTRODUCTION

β -blockers are integral in the treatment of cardiovascular disease. Despite their proven benefits, β -blockers are avoided in asthmatics due to concerns about bronchoconstriction.¹ These concerns led to a consensus statement from the European Society of Cardiology stating that a history of asthma should be considered a contraindication to the use of any β -blocker.²

Evidence now suggests that cardioselective β -blockers can be given relatively safely to patients

with a history of obstructive airway disease.³ However, β -blockers regardless of selectivity are seldom used in such patients.⁴

Several safety issues are likely to influence the prescription of β -blockers in asthma. In addition to potential bronchoconstriction upon first exposure, subsequent up-titration of β -blockers results in further exposure and potential risk. Up-titration is commonly performed in the community and without direct medical supervision. Moreover the presence of β_2 adrenoceptor antagonism might conceivably attenuate the response to concomitant β -agonist inhaled treatment.

The concern about β -blocker use in asthma led partly to the development of ivabradine as an alternative negatively chronotropic medication, which does not result in any bronchoconstriction when used in asthma.⁵ The mechanism of β -blocker induced bronchoconstriction is thought to be due to the effects of β_2 adrenoceptor antagonism uncovering the prevailing cholinergic tone via post-junctional smooth muscle muscarinic type 3 adrenoceptors, resulting in airway smooth muscle constriction.⁶ Oxitropium, a muscarinic antagonist, has previously been shown to prevent acute propranolol induced bronchoconstriction.⁷ Previous open label studies have suggested a potential therapeutic role for the non-selective β -blocker nadolol in asthmatics, with an improvement in airway hyper-responsiveness (AHR) being seen.^{8–9} Although we failed to see any beneficial effects on AHR with propranolol,¹⁰ the data generated allow us to also evaluate the safety and tolerability of propranolol in asthma. In this study, before randomisation, a subgroup of participants were given a single intravenous (iv) injection of the cardioselective β -blocker esmolol and the effects on pulmonary function were assessed.

We present our experience of both cardioselective (iv) and non-selective (oral) β -blocker use in asthma. We first assessed the pulmonary effects of acute iv esmolol dosing, before assessing the effects of first dose exposure to oral propranolol and the subsequent effects at dose up-titration, in the presence of concurrent tiotropium.

METHODS

A post-hoc analysis of a double blind, randomised, placebo controlled trial of propranolol in mild-to-moderate asthmatics was performed.¹⁰ The Tayside Medical Research Ethics Committee gave approval before commencement of the trial

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(10/S0501/22). The study was registered with <http://www.clinicaltrials.gov> (NCT01074853).

Mild-to-moderate asthmatics aged between 18–65 years, with forced expiratory volume in 1 s (FEV₁) >80% predicted and diurnal FEV₁ variation <30%, and taking inhaled corticosteroid (≤ 1000 µg/day beclomethasone dipropionate equivalent dose), were recruited. Participants were required to demonstrate AHR to methacholine bronchial challenge PC₂₀<8 mg/mL. Participants were all non-smokers. Exclusion criteria included: asthma exacerbation within the last 6 months, systolic blood pressure <110 mm Hg, heart rate <60 beats/min (bpm), history of arrhythmias, and concurrent negative chronotropic medications.

Before randomisation a subgroup of participants underwent a safety visit and received a single iv bolus dose of esmolol (0.5 mg/kg). Spirometry, impulse oscillometry (IOS), heart rate, and blood pressure were recorded pre- and post-acute esmolol dosing at 2, 8, 16, and 32 min (figure 1).

Participants then underwent dose titration of propranolol or matched placebo at weekly intervals (10 mg twice daily, 20 mg twice daily, 80 mg long acting (LA) once daily) as tolerated over a 2–4 week period. Following the first dose of propranolol (or matched placebo) at 10 mg, and at every subsequent up-titration visit (ie, the first dose exposure to 20 mg and 80 mg), participants were observed within the department for 3 h with serial pulmonary function, heart rate, and blood pressure recorded. Tiotropium was given concurrently during the dose titration period with propranolol (or matched placebo). The full methods of the main protocol have been described in detail elsewhere¹⁰; here we only report on the subgroup of patients who received initial iv esmolol in addition to their propranolol up-titration data.

Outcome measures

The main outcome measures were the effects on pulmonary function following acute esmolol and propranolol use. Spirometry and IOS were recorded.

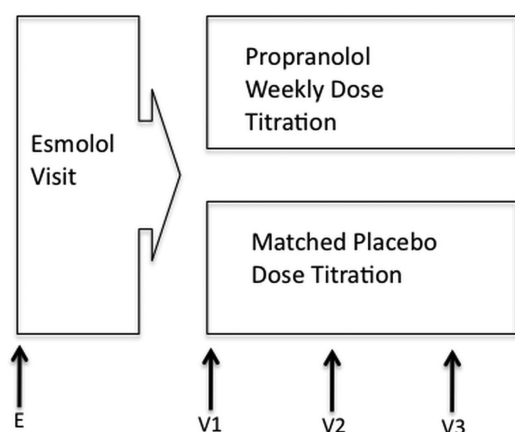


Figure 1 Study diagram. E: Esmolol visit. Single dose of intravenous (iv) esmolol 0.5 mg/kg. Spirometry, impulse oscillometry (IOS), blood pressure (BP), and heart rate (HR) measured pre-dose and at 2, 8, 16, and 32 min post-dose. V1: Observed first dose of 10 mg of oral propranolol or matched placebo. Spirometry, IOS, BP, and HR measured pre- and 3 h post-dosing. V2: Observed first dose of 20 mg of oral propranolol or matched placebo. Spirometry, IOS, BP, and HR measured pre- and 3 h post-dosing. V3: Observed first dose of 80 mg of oral propranolol or matched placebo. Spirometry, IOS, BP, and HR measured pre- and 3 h post-dosing.

Measurements

Spirometry and IOS were performed in accordance with published guidelines.^{11 12} A SuperSpiro Spirometer (Micro Medical, UK) and IOS Jaeger Masterscreen (Germany) were used. Bronchoconstriction was indicated as either a fall in forced expiratory lung volume (FEV₁) or an increase in total airway resistance at 5 Hz (R5). Asthma control questionnaires were performed.¹³

Statistical analysis

Data were assessed for normality with the Shapiro-Wilk test and Box plots. The primary outcome was change in FEV₁ post-esmolol administration. For all outcomes, comparisons were made by a multifactorial analysis of variance model with Bonferroni corrections for pairwise comparisons. All analyses were performed using SPSS V.21 (Chicago, Illinois, USA).

RESULTS

Sixteen participants completed the main study, of which the first 12 enrolled participants (seven female, five male) underwent both esmolol and propranolol dosing and were used for the present analysis. No participant who received esmolol failed to be randomised and subsequently each participant received propranolol. Mean age (SEM) was 37 (5). Baseline characteristics are shown in table 1.

Acute cardioselective β -blockade: effects on pulmonary function

Pulmonary function was assessed pre-esmolol dosing and post-esmolol dosing at 2, 8, 16, and 32 min. No significant differences were seen in FEV₁% predicted following an intravenous esmolol bolus. Mean changes in FEV₁% predicted (95% CI) were: 2 min post-esmolol, −0.58% (−2.96 to 1.79), $p=0.99$; 8 min, 0.42% (−3.17 to 4.00), $p=0.99$; 16 min, 0.75% (−2.73 to 4.22), $p=0.99$; and 32 min, 0.67% (−3.51 to 4.85), $p=0.99$ (figure 2).

No significant differences were seen in total airway resistance as R5% predicted post-esmolol. Mean changes in R5% predicted (95% CI) were: 2 min post-esmolol, 1.6% (−12.65 to 9.44), $p=0.99$; 8 min, 1.85% (−12.49 to 8.78), $p=0.99$; 16 min, −0.51% (−13.43 to 12.40), $p=0.99$; and 32 min, −1.1% (−11.64 to 9.44), $p=0.99$.

Acute cardioselective β -blockade: effects on blood pressure and heart rate

Significant reductions in heart rate were seen at 2 and 32 min post-esmolol dosing. Mean falls in heart rate (95% CI) were: 2 min post-esmolol, −4.7 bpm (−7.9 to −1.3), $p=0.002$; and 32 min, −4.4 bpm (−7.8 to −1.1), $p=0.003$. A significant small reduction was also seen in systolic blood pressure at 2 and 32 min post-esmolol dosing. Mean falls in systolic blood pressure (95% CI) were: 2 min post-esmolol, −5.9 mm Hg (−11.4 to −0.41), $p=0.03$; and 32 min, −5.7 mm Hg (−11.2 to −0.17), $p=0.04$.

Acute non-selective β -blockade with concurrent tiotropium: effects on pulmonary function

A non-significant increase in FEV₁% predicted was seen 30 min post 10 mg propranolol (with tiotropium); mean difference (95% CI) 3.9% (−0.4 to 8.2), $p=0.084$; 1 h post-dose, 3.8% (−1.3 to 8.8), $p=0.26$; 2 h post-dose, 3.3% (−2.6 to 9.1), $p=0.80$; and 3 h post dose, 3.3% (−3.6 to 10), $p=1.0$ (figure 3).

Table 1 Demographics

Subject/sex	Age (years)	FEV ₁ %	FEV ₁ /FVC ratio	Methacholine PC ₂₀ (mg/mL)	BDP equivalent daily dose (µg)	Concurrent medications: LABA (L), antihistamine (A), LTRA (LT), nasal spray (NS)
1/F	21	92	0.78	0.92	400	L, A, NS
2/F	64	99	0.71	2.48	400	L, LT, NS
3/F	31	85	0.75	0.99	500	A, LT
4/M	48	85	0.68	2.0	500	L, LT
5/F	65	103	0.69	0.71	200	—
6/M	29	98	0.71	1.36	100	—
7/M	57	106	0.81	3.45	1000	NS
8/M	20	91	0.76	3.71	400	—
9/F	19	91	0.83	0.67	400	A
10/M	19	90	0.85	1.73	200	A
11/F	25	91	0.85	2.4	200	A
12/F	50	88	0.67	1.13	400	A, NS
Mean (SEM)	37 (3)	93 (2)	0.76 (0.02)	1.54 (1.06 to 2.23)*	392 (67)	

*Data displayed as geometric mean (95% CI). Data shown as % predicted for age, gender, race.

BDP, beclomethasone dipropionate; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; LABA, long acting β-agonist; LTRA, leukotriene receptor antagonist.

Falls in R5% predicted were seen at 30 min post 10 mg propranolol (and tiotropium); mean difference (95% CI) −39.3% (−69.9 to −8.8), $p=0.009$; 1 h post-dose, −32.8% (−58.8 to −6.8), $p=0.01$; 2 h post-dose, −31.3% (−58.2 to −4.3), $p=0.01$; and 3 h post-dose, −35.8% (−72.5 to 9.5), $p=0.06$.

Compared to matched placebo there were no significant differences observed in FEV₁% and R5% predicted 3 h post 10 mg of propranolol in the presence of concurrent tiotropium (table 2).

Up-titration of non-selective β blockade with concurrent tiotropium

No evidence of bronchoconstriction was demonstrated in either FEV₁% or R5% predicted following first dose exposure to either the 20 mg or 80 mg dose of propranolol in the presence of concurrent tiotropium (figure 4).

Mean increase in FEV₁% predicted (95% CI) 30 min post 20 mg of propranolol (with tiotropium) was 0.33% (−1.6 to 2.3), $p=0.99$; and 3 h post-dose, 1.3% (−1.6 to 4.1), $p=0.99$. Mean fall in R5% predicted (95% CI) 30 min post 20 mg of

propranolol (with tiotropium) was −4.0% (−17.8 to 9.7), $p=0.99$; and 3 h post dose, −7.7% (−21.7 to 6.2), $p=0.80$.

Mean increase in FEV₁% predicted (95% CI) 30 min post 80 mg of propranolol (with tiotropium) was 0.92% (−1.26 to 3.09), $p=0.99$; and 3 h post dose, 1.25% (−3.56 to 6.06), $p=0.99$. Mean fall in R5% predicted (95% CI) 30 min post 80 mg of propranolol (with tiotropium) was −5.5% (−20.3 to 9.2), $p=0.99$; and 3 h post dose, −7.2% (−28.9 to 14.5), $p=0.99$.

Compared to matched placebo there were no significant differences observed in FEV₁% and R5% predicted in the presence of tiotropium, except for after the 80 mg dose of propranolol for R5% which amounted to a mean difference of 9.4%, $p=0.03$ (table 2).

Asthma control

At study baseline the mean asthma control questionnaire score (95% CI) was 0.92 (0.59 to 1.26). Post-chronic propranolol dosing with 80 mg, the mean value was 1.01 (0.68 to 1.47). There was no significant difference in asthma control compared

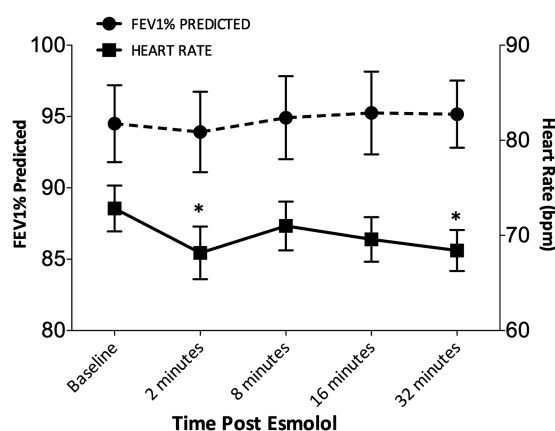


Figure 2 Effect of esmolol on FEV₁% predicted and heart rate. Data shown as % predicted for age, gender, race. Data displayed as mean (SEM). *Significant difference from baseline $p<0.05$. Bronchoconstriction is reflected as a fall in FEV₁ using spirometry. FEV₁, forced expiratory volume in 1 s.

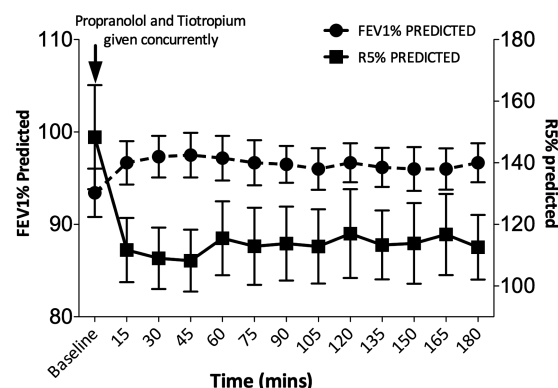


Figure 3 Protective pulmonary effects of tiotropium post 10 mg dose of propranolol. Data shown as % predicted for age, gender, race. Data displayed as mean (SEM). Bronchoconstriction is reflected as either a fall in FEV₁ using spirometry or an increase in R5 using impulse oscillometry. FEV₁, forced expiratory volume in 1 s; R5, total airway resistance at 5 Hz.

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Table 2 Effects of acute dosing of propranolol versus placebo on pulmonary function (with concurrent tiotropium)

	Propranolol (mean, 95% CI)	Placebo (mean, 95% CI)	p Value		Propranolol (mean, 95% CI)	Placebo (mean, 95% CI)	p Value
<i>FEV₁% predicted</i>				<i>R5% predicted</i>			
3 h post 10 mg dose	96.7 (92 to 101.3)	100.5 (94.1 to 106.9)	0.18	3 h post 10 mg dose	112.6 (89.5 to 135.7)	111.7 (84 to 139.4)	0.91
3 h post 20 mg dose	96.9 (91.8 to 102)	100.6 (93.5 to 107.6)	0.12	3 h post 20 mg dose	109.4 (91.6 to 127.3)	102.3 (73.9 to 130.6)	0.32
3 h post 80 mg dose	97.1 (91.4 to 102.7)	99.7 (93.5 to 105.8)	0.09	3 h post 80 mg dose	109.7 (87.9 to 131.5)	100.3 (76.4 to 124.1)	0.03

Data shown as % predicted for age, gender, race.

FEV₁, forced expiratory volume in 1 s; R5, total airway resistance at 5 Hz.

with placebo, mean value 0.87 (0.51 to 1.23), the mean difference being 0.14 (−0.31 to 0.60), $p=0.5$.

Non-selective β -blockade: effects on heart rate and blood pressure

Heart rate (95% CI) fell significantly 3 h post 10 mg of propranolol, −11 bpm (−15 to −7), $p<0.001$; post 20 mg of propranolol, −6 bpm (−10 to −1), $p=0.013$; and post 80 mg of propranolol, −7 bpm (−15 to −1), $p=0.049$.

No significant change was seen in supine systolic blood pressure post 10 mg of propranolol, mean difference (95% CI) 2 mm Hg (−3 to 7), $p=0.40$; post 20 mg of propranolol, 2 mm Hg (−4 to 7), $p=0.53$; and post 80 mg of propranolol, 4 mm Hg (−2 to 9), $p=0.19$.

DISCUSSION

β -blockers are avoided in asthma due to concerns over possible bronchoconstriction. The aim of the present study was to assess the effects on pulmonary function of both cardioselective and non-selective β -blockade. Esmolol is highly cardioselective in exhibiting a 34-fold higher affinity for β_1 versus β_2 adrenoceptors.¹⁴ This, along with the short duration of action of esmolol (half-life of 9 min), makes it ideally suited for assessing safety in asthma. As part of our initial study protocol, we decided that if an individual demonstrated significant adverse pulmonary effects with iv esmolol, they would not proceed to oral propranolol.

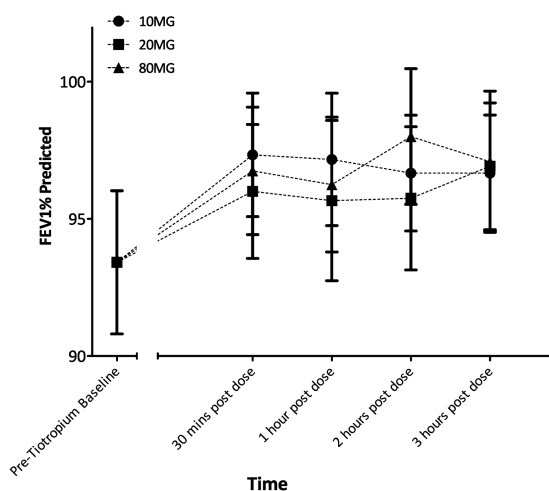


Figure 4 Protective effects of tiotropium on FEV₁% predicted at propranolol up-titration. Data shown as % predicted for age, gender, race. Data displayed as mean (SEM). Bronchoconstriction is reflected as a fall in FEV₁ using spirometry. FEV₁, forced expiratory volume in 1 s.

We have demonstrated that in a cohort of stable mild-to-moderate asthmatics, acute dosing with iv esmolol results in no significant adverse effects on pulmonary function, despite evidence of systemic β_1 -blockade with reduced heart rate and blood pressure. Given that iv esmolol avoids first pass inactivation we are reassured by the lack of acute bronchoconstriction. While the use of a forced expiratory manoeuvre with spirometry (FEV₁) is considered the gold standard method for assessing airway calibre, IOS provides a novel alternate effort independent technique.¹² We have previously shown IOS to be a more sensitive marker than spirometry for the assessment of β -blocker induced bronchoconstriction,¹⁵ and thus it is reassuring to find no significant adverse effects on R5% predicted following acute esmolol dosing. Our findings support previous evidence that iv esmolol can be given safely in cases of mild-to-moderate asthma.¹⁶

We have previously shown that acute propranolol dosing of 10 or 20 mg in a cohort of mild-to-moderate controlled asthmatics results in a mean 4.7% reduction in FEV₁% predicted and a mean 31.3% increase in R5% at 2 h after propranolol dosing.¹⁷ In our current study we have shown that by means of concurrent inhaled tiotropium administration, we saw no significant worsening of FEV₁% predicted or R5% predicted following first dose exposure with 10 mg of propranolol. By demonstrating significant reductions in supine heart rate 3 h post-propranolol we have clear evidence of systemic cardiac β_1 adrenoceptor blockade.

It is well recognised that achieving optimal dosing of β -blockers in clinical practice is challenging, with the tolerated doses of β -blockers used in clinical practice often being substantially less than recommended.¹⁸ Although lack of dose optimisation is likely to be due to multifactorial reasons, it may be assumed that dose intolerance and contraindications may have influenced β -blocker dosing. In asthmatics prescribed β -blockers, it is even more unlikely that dose optimisation will be achieved due to clinical concerns about bronchospasm.

We have shown that up-titration of propranolol can be achieved in asthma, without any significant deterioration in FEV₁% or R5% predicted at the time of first dose or up-titration in the presence of concomitant tiotropium use. Furthermore we have shown no worsening of the asthma control questionnaire with propranolol versus matched placebo.

Our study was originally designed to investigate the proposed therapeutic benefits of non-selective β -blockade in asthma.¹⁹ Whilst we failed to show any therapeutic benefits, our results allowed us to evaluate the safety of non-selective β -blockade in asthma. On the basis of our data with oral propranolol, we are not advocating that asthmatic patients should be given non-selective β -blockers with tiotropium cover, when a cardioselective oral agent such as bisoprolol is more likely to be tolerated, especially in the presence of inhaled tiotropium. Indeed recent

data have indicated a role for regular tiotropium for use as long acting controller therapy in addition to inhaled corticosteroids.²⁰ However, we believe that our results raise the possibility that if a non-selective β -blocker such as propranolol can potentially be tolerated in asthma, then so may a cardioselective β -blocker, thus potentially offering reassurance to those wishing to utilise the cardiovascular benefits of β -blockers in patients with asthma controlled on inhaled corticosteroids. We cannot extrapolate our data to what might occur in patients with more severe disease.

The potential for adverse effects with β -blocker use would be dependent upon the selectivity of the drug chosen. When comparing the selectivity ratios of the β -blockers for human β_1 and β_2 adrenoceptors, the affinity of propranolol is 8.3-fold higher at the β_2 than β_1 adrenoceptor.²¹ This is in comparison with examples of the so called cardioselective β -blockers including metoprolol (2.3-fold affinity β_1 versus β_2) and bisoprolol (13.5-fold affinity β_1 versus β_2 receptors).²¹ Thus, on the basis that our asthmatic patients tolerated iv esmolol and oral propranolol, one might expect that they would also be able to tolerate oral bisoprolol, especially when given in gradual dose increments in addition to tiotropium cover.

When assessing the benefits of β -blocker use in the treatment of cardiovascular disease, asthmatic patients have generally not been studied due to the reluctance to use β -blockers in these patients. However, when reviewing evidence of β -blocker use within another contraindicated group of patients who have more severe impairment of pulmonary function, namely chronic obstructive pulmonary disease, reduced mortality rates have been associated with β -blocker use.^{22–23} It is unclear whether these benefits would be seen in an asthmatic population; however, limited evidence does suggest a reduction in 2 year mortality with β -blocker use post-myocardial infarction.²⁴

CONCLUSION

We have shown that acute esmolol did not cause any worsening of pulmonary function in controlled mild-to-moderate asthmatics. Furthermore, first dose exposure and subsequent up-titration with propranolol up to 80 mg was achieved without any significant adverse impact on pulmonary function, due to concurrent administration of the long acting muscarinic antagonist tiotropium. Further studies are now warranted to determine whether chronic cardioselective β -blockade such as bisoprolol can be achieved safely in persistent asthmatics, especially with concurrent tiotropium during up-titration, thereby providing the means for potentially improving treatment of cardiovascular disease in an otherwise contraindicated cohort.

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Competing interests None.

Ethics approval Tayside Medical Research Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The corresponding author had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

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