Tolerability of Bisoprolol on Domiciliary Spirometry in COPD

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Abstract:	We investigated if serial domiciliary measures of spirometry were sensitive at detecting subtle effects of beta-2 blockade associated with bisoprolol in (n=17) patients with COPD. After a two week run in on inhaled corticosteroid (ICS) and long acting beta-2 agonist (LABA): beclometasone/formoterol 100/6µg, patients' started additional a long acting muscarinic receptor antagonist: (LAMA) Tiotropium 18µg, with concomitant weekly dose titration of bisoprolol: 1.25mg-2.5mg-5mg. After a further week of bisoprolol 5mg, they were stepped back down to (ICS/LABA) for one week. Mean age was 64 years, mean FEV1 52% predicted, and mean FEV1/FVC ratio of 0.46. Compared to baseline am FEV1 of 1.38L (95% CI 1.14-1.61L), both ICS/LABA/LAMA and ICS/LABA in conjunction with bisoprolol showed statistically significant mean falls of 100ml (1.28L, 95% CI 1.03-1.53L), and 120ml respectively (1.26L, 95% CI 1.01-1.51L); equalling and exceeding the MCID of 100ml respectively. These changes were disconnected from symptoms, reliever use and oxygen saturation.

Tolerability of bisoprolol on domiciliary spirometry in COPD

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Abstract:

We investigated if serial domiciliary measures of spirometry were sensitive at detecting subtle effects of beta-2 blockade associated with bisoprolol in (n=17) patients with COPD.

After a two week run in on inhaled corticosteroid (ICS) and long acting beta-2 agonist (LABA): beclometasone/formoterol 100/6µg, patients' started additional a long acting muscarinic receptor antagonist: (LAMA) Tiotropium 18µg, with concomitant weekly dose titration of bisoprolol: 1.25mg-2.5mg-5mg. After a further week of bisoprolol 5mg, they were stepped back down to (ICS/LABA) for one week.

Mean age was 64 years, mean FEV_1 52% predicted, and mean FEV_1/FVC ratio of 0.46. Compared to baseline am FEV_1 of 1.38L (95% CI 1.14-1.61L), both ICS/LABA/LAMA and ICS/LABA in conjunction with bisoprolol showed statistically significant mean falls of 100ml (1.28L, 95% CI 1.03-1.53L), and 120ml respectively (1.26L, 95% CI 1.01-1.51L); equalling and exceeding the MCID of 100ml respectively. These changes were disconnected from symptoms, reliever use and oxygen saturation.

Introduction:

There is a reluctance to prescribe beta-blocker therapy to patients with COPD and cardiovascular disease, even with cardioselective drugs, due to concerns of potential bronchoconstriction (1, 2). Accumulating evidence however, suggests that more commonly used cardioselective agents such as bisoprolol do not negatively impact upon laboratory based measures of pulmonary function, such as the forced expiratory volume in 1 second (FEV_1), in patients with COPD (3).

Whether the pulmonary tolerability of beta-blockers is interdependent with concomitant inhaled therapy, however, is yet to be established. Therefore it is important to dissect out the relative contribution of long acting beta-2 agonist (LABA) with or without long acting muscarinic receptor antagonists (LAMA), in terms brochoprotection against a small degree of potential beta-2 receptor antagonism with bisoprolol.

It would seem logical that a high affinity LABA, such as formoterol, would competitively displace a beta-1 selective beta-receptor antagonist such as bisoprolol, which exhibits weaker binding affinity for the beta-2 receptor (4). In vivo however, it has previously been demonstrated that bisoprolol even at a dose of 5mg significantly blunts the beta-2 mediated response to isoprenaline, albeit to a lesser than non-selective drugs (5). Moreover, as M3 muscarinic receptors are known to be involved in mediating bronchoconstriction with beta-blockers the addition of LAMA might be expected to confer additional protection in terms of pulmonary tolerability of bisoprolol in patients with COPD. In this regard non-selective beta blockers such as carvedilol are not used on a routine basis for patients with COPD.

Furthermore, given that COPD is characterised by persistent symptoms and airflow limitation, a conventional spot measure of FEV_1 done in a laboratory setting may not pick up more subtle adverse effects of bisoprolol as compared to serial domiciliary testing.

Methods:

A previous proof of concept study (6) (NCT01656005) prospectively studied patients aged 40-80 years, with GOLD B and C stage COPD, who in brief after a two week run in on inhaled corticosteroid (ICS) and LABA as beclometasone/formoterol 100/6µg (Fostair, Chiesi, Manchester , UK) 2 puffs bid , started concomitant weekly dose titration with bisoprolol (1.25mg-2.5mg-5mg). They were then were placed on triple inhaler therapy with ICS/LABA/LAMA as Fostair with Tiotropium (Spiriva Handihaler, Boehringer Ingelheim, Bracknell ,UK) 18µg od for 1

week ,and then stepped down again to ICS/LABA (Fostair) for a further week. This study was approved by the East of Scotland Regional Ethics Committee (12/ES/0054), and completed at Ninewells Hospital, Dundee, UK.

Here we report on unpublished data in a subgroup of 17 patients in which domiciliary measurements were available, comprising daily FEV_1 and forced expiratory volume in 6 seconds (FEV_6), an acceptable surrogate for forced vital capacity in COPD (7) ,measured with a Piko-6 digital lung function meter (Nspire ,Hertford ,UK). Patients were issued paper diary cards during which they noted their daily global symptom score on a scale of 0-3. This represented their overall COPD symptoms that day and was rated from 0=none, 1=mild, 2=moderate, 3=severe. This allowed patients to consider their symptoms in context to their daily lives, activities and environment. Domiciliary resting heart rate and oxygen saturation were also measured, by a pulse oximeter (Merlin M-Pulse Lite, Merlin Medical, Rhymney, UK). The impact of bisoprolol 5mg OD was compared while receiving concomitant ICS/LABA/LAMA and ICS/LABA verses pre beta-blocker baseline (while taking ICS/LABA).

We analysed the last 4 days of values (which were time averaged) prior to taking bisoprolol (baseline) as well as while taking bisoprolol with either dual or triple inhaled therapy. These were then compared using repeated measures ANOVA with post hoc Bonferroni correction to obviate confounding the overall alpha error by multiple pairwise comparisons ($P<0.05$ two tailed) .

Results:

80% of the patients were male, with a mean age of 64 years, mean FEV_1 52% predicted, mean FEV_1/FVC ratio of 0.46, mean 50 pack year smoking history, and 7% mean FEV_1 reversibility to salbutamol 400µg. Results are presented in table 1. Compared to baseline, both ICS/LABA/LAMA and ICS/LABA in conjunction with bisoprolol were associated in similar mean falls in morning domiciliary FEV_1, amounting to means of 100ml and 120ml respectively. There was no statistically significant difference between ICS/LABA/LAMA and ICS/LABA while taking bisoprolol for either FEV_1 or FEV_6. Despite bisoprolol producing a mean domiciliary heart reduction of 11 beats/min, there was no significant decline in oxygen saturation compared to baseline. Moreover the mean symptom score did not change while taking bisoprolol, remaining at a mild level. There was also no significant difference in reliever use with salbutamol pre or post beta blocker. We observed no significant correlation between either peripheral blood eosinophil count (mean 215 (95%CI 154-275) cells/µl) or reversibility to salbutamol and percentage fall in domiciliary FEV_1 or FEV_6 whilst taking bisoprolol (figure).

Discussion

Our results showed that the effect of bisoprolol on domiciliary morning FEV_1 was not only statistically significant but also equalled (with ICS/LABA/LAMA) or exceeded (with ICS/LABA) the minimal clinically important difference value of 100ml (8) . We were surprised to find such an effect as we previously did not detect any significant impact on laboratory spot FEV1 measurement with bisoprolol in conjunction with either dual (mean FEV_1 fall of 10ml) or triple concomitant inhaler therapy (mean FEV_1 increase of 30ml) . This illustrates the superior sensitivity of measuring serial domiciliary lung function for detecting more subtle changes associated with bisoprolol in COPD. However despite the reductions in FEV_1 and corroborating reduction in resting heart rate (due to beta-1 blockade) , there was no associated change in either salbutamol use, symptom score or oxygen saturation. This in turn infers there is a disconnect between FEV_1 and FEV_6 from either symptoms or gas exchange. The corollary being that a small decline in lung function may have little real life impact on patients being prescribed beta blocker therapy. Alternatively another viewpoint may be that lowering resting heart rate resulted in patients experiencing less dyspnoea throughout the day. Our study demonstrated a reduction in resting heart rate from 80 bpm to 69 bpm after bisoprolol; COPD patients with heart rates <75 bpm have a decreased cardiovascular mortality versus those with a heart rate ≥75 (9).

Bisoprolol is highly selective with a 14:1 ratio for β1 to β2 receptor affinity (10). However it is well recognised that although there may be dose related airways related beta-2 blockade with cardioselective drugs ,it is still considerably less than with non selective agents (11). In terms of trying to identify the potential impact of an asthmatic component of COPD on beta-2 blockade with bisoprolol, we did not observe any relationship of FEV_1 fall to blood eosinophils or salbutamol reversibility.

The failure of concomitant tiotropium as inhaled triple therapy to confer protection against bronchoconstriction with bisoprolol was surprising. However we appreciate that we did not have a baseline value for comparison while taking ICS/LABA/LAMA to assess the relative bronchodilator impact of tiotropium in the absence of bisoprolol. Another limitation of this proof of concept study is the small sample size, and that there was no placebo arm to compare with bisoprolol but only a baseline value while taking ICS/LABA. Finally, our study duration was not sufficiently long enough to assess the impact of beta blocker therapy on exacerbations.

In summary our study demonstrates that in the context of single or dual long acting bronchodilator therapy , the beta-1 selective antagonist bisoprolol was associated with subtle but significant

falls in domiciliary FEV_1 ,which were disconnected from symptoms ,reliever use and oxygen saturation. Trials are now underway in COPD to evaluate the effects of bisoprolol on cardiopulmonary exercise testing (ClinicalTrials.gov NCT02380053) as well as to assess the impact on COPD exacerbations.

Figure Legend:

Correlation of percentage change in forced expiratory volume in one second (FEV_1: top), and in six seconds (FEV_6 bottom), and eosinophil counts. P=ns, no relationship observed.

Conflict of Interest: Dr. Jabbal reports personal fees and non-financial support from Chiesi Pharma, personal fees and non-financial support from Pfizer, non-financial support and other from Napp, personal fees and non-financial support from AstraZeneca, personal fees from Boehringer Ingelheim, non-financial support from TEVA, outside the submitted work. Dr. Lipworth reports grants, personal fees and non-financial support from Chiesi, grants, personal fees, non-financial support and other from Boerhingher Ingelheim, grants and personal fees from Meda , grants, personal fees and non-financial support from Teva , grants from Janssen, grants from AstraZeneca, grants from Roche, personal fees from Dr Reddys , personal fees from Cipla, personal fees from Lupin, personal fees from Sandoz, grants from Sanofi , outside the submitted work.

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Figure

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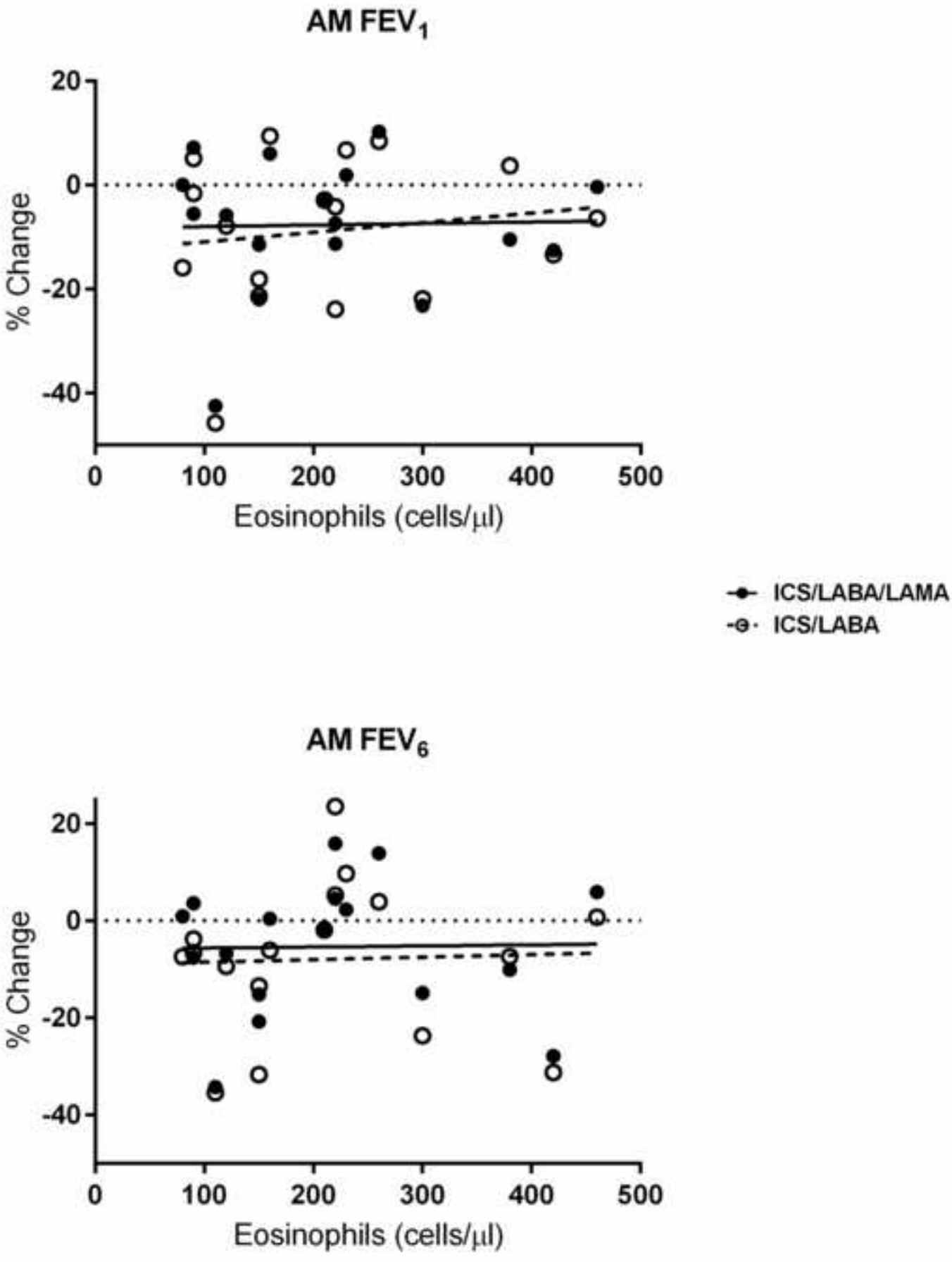

Table 1. Results of domiciliary measures

	BASELINE (OFF BISOPROLOL)	ICS/LABA/LAMA (+BISOPROLOL)	ICS/LABA (+BISOPROLOL)
FEV1 AM (L)	1.38 (1.14- 1.61)	1.28 (1.03- 1.53)*	1.26 (1.01- 1.51)*
FEV1 PM (L)	1.38 (1.12- 1.63)	1.32 (1.06- 1.57)	1.29 (1.04- 1.54)*
FEV6 AM (L)	2.46 (2.06- 2.85)	2.33 (1.90-2.25)	2.27 (1.84-2.69)
FEV6 PM (L)	2.50 (2.12-2.89)	2.39 (1.98- 2.80)	2.33 (1.92-2.74)*
SYMPTOMS AM	0.27 (-0.21- 0.55)	0.28 (-0.48- 0.51)	0.34 (0.10- 0.57)
SYMPTOMS PM	0.28 (-0.08- 0.57)	0.40 (0.16- 0.63)	0.47 (0.17-0.77)
RELIEVER USE AM	0.6 (0.2- 1.3)	0.8 (0.2- 1.7)	1.0 (0.1- 2.0)
RELIEVER USE PM	1.7 (0.2-3.3)	1.5 (0.2-2.8)	1.9 (0.4- 3.4)
HEART RATE (BPM)	80 (74-85)	69 (64-73)*	69 (65-73)*
SP02 (%)	96 (95-97)	95 (94-97)	96 (95-97)

Domiciliary data are presented as means and 95% CI. *P<0.05 vs pre beta-blocker baseline while taking bisoprolol and concomitant ICS/LABA or ICS/LABA/LABA. Reliever use equates to puffs of salbutamol. No difference was observed between ICS/LABA/LAMA and ICS/LABA while taking bisoprolol.