



Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Letters to the Editor

Obstructive lung diseases and beta-blockers: Where do we stand?*

Keywords:

Asthma
Atrial fibrillation
Beta-blocker
Chronic obstructive pulmonary disease
Coronary artery disease
Heart failure

Cardiovascular diseases are major public health problems. β -blockers therapy is indicated for the majority of patients with heart failure and coronary artery disease (Class I, Level of Evidence: A). These drugs are also first-line therapy for atrial fibrillation. However, β -blocker use continues to be less than optimal, principally in patients with concomitant chronic obstructive lung diseases, such as asthma and chronic obstructive pulmonary disease (COPD).

Historically, studies suggested that β -blockers increased airway hyperresponsiveness and competed with β_2 -agonists, thus theoretically increasing the risk of adverse pulmonary outcomes. Cardioselective β -blockers have been designed to target β_1 -adrenoreceptors (AR) while avoiding β_2 AR in the lung and elsewhere. However, these so called cardioselective β -blockers are only relatively selective and exert significant β_2 antagonism at therapeutic doses, though to a lesser extent than non-selective β -blockers. Thus, it might seem counterintuitive to prescribe both β -blockers and β -agonists in the same patient, even when they are targeting different organs. As a result, β -blockers are often withheld or discontinued from patients with asthma or COPD, especially in the setting of acute exacerbations.

Despite these concerns, evidence supports that chronic use of cardioselective β -blockers do not cause an increase of exacerbations, reduction in airway function or worsening of quality of life in patients with cardiovascular and obstructive pulmonary diseases.

A meta-analysis of randomized controlled trials evaluating acute β -blocker exposure in asthma showed that selective β -blockers caused a mean reduction in forced expiratory volume in one second (FEV_1) of -6.9% (95% confidence interval (CI), -8.5 to -5.2) [1]. However, this change in FEV_1 did not translate into symptoms. A dose–response relationship was demonstrated for atenolol, bisoprolol and metoprolol. Additionally, subgroup analysis suggested heterogeneity in treatment effect of different selective β -blockers, as celiprolol did not cause statistically significant changes in FEV_1 [1].

Another systematic review of 22 randomized trials to evaluate the effects of cardioselective β -blockers in patients with COPD showed no significant change in respiratory symptoms or spirometry parameters, when these drugs were given in a single dose or for a longer duration

(up to 16 weeks) [2]. The FEV_1 did not change significantly nor did the response to β_2 -agonist treatment. Subgroup analyses revealed no significant change in results for those participants with severe airways obstruction or those with concomitant cardiovascular disease. These authors also broadly analysed the effect of cardioselective β -blockers on respiratory function of patients with asthma or COPD with a reversible obstructive component [3]. Although the first dose of a β -blocker produced a small decrease in FEV_1 (-7.5% , 95% CI -9.3 to -5.6), this was not associated with an increase in symptoms. Importantly, continuing therapy from three days to four weeks produced no significant change in FEV_1 , symptoms or inhaler use, compared to placebo.

It is interesting to note that a significant improvement in the response to inhaled salbutamol was seen with β -blocker treatment, suggesting an increased effect of β_2 -agonist stimulation [3]. More recently, after encouraging results in murine studies, the first proof-of-concept open-label study in humans was set to evaluate the safety and effect of β -blockers for the potential treatment of asthma. It showed that chronic dose-escalating non-selective β -blocker nadolol use in patients with steroid-naïve mild asthma was not only safe but could have beneficial effects on airway hyperresponsiveness [4]. Indeed, in eight out of the ten subjects evaluated, nine weeks of beta-blocker treatment produced a significant, dose-dependent increase in the methacholine PC20. Moreover, a large retrospective cohort study suggested that besides being well tolerated by patients with COPD, β -blockers could reduce the risk of exacerbations and mortality, when added to established inhaled stepwise therapy, independent of overt cardiovascular disease and cardiac drugs [5]. No significant adverse effects on pulmonary function were observed. A recent meta-analysis of observational studies supported these results [6]. Taken together, these observations suggest that β -blockers may have independent beneficial effects in obstructive lung diseases. One possibility is that up-regulation of β_2 AR by chronic β -blockade may improve the effectiveness of β_2 -agonists [5,7]. In this regard, no adverse effect was observed with the addition of β -blockers to treatment regimens that included long-acting β -agonists [5]. Moreover, co-administration of long-acting anti-muscarinic drugs may be beneficial to prevent β -blocker induced bronchoconstriction. This would suggest a rationale for using tiotropium when prescribing a β -blocker for a patient with obstructive pulmonary disease [5,7].

After these studies, the effect of chronic nonselective β -blockade was assessed as add-on to inhaled corticosteroids in patients with stable persistent asthma [8]. The authors reported no significant effect of propranolol compared with placebo on airway hyperreactivity, with no significant change in asthma control or quality of life but only partial attenuation of acute salbutamol recovery after challenge. These at first sight discouraging results raised noteworthy discussion regarding the importance of β -blockers differential pharmacodynamics and β_2 AR signalling in asthma [9]. The β_2 AR signals *via* at least two independent pathways: the G protein cyclic adenosine monophosphate (Gs-cAMP) pathway, and the β -arrestin and/or extracellular signal-regulated kinases (ERK) activation. The endogenous ligand for the β_2 AR, epinephrine, and β_2 AR agonists used in asthma or COPD therapy, like salmeterol

* The authors declare no conflicts of interest related to this study.

and formoterol, activate both pathways. However, studies into the mechanisms mediating the efficacy of β -blockers point to differential "ligand bias", *i.e.*, the ligand ability to selectively promote specific intracellular signalling events [9,10]. Several *in vitro* and *in vivo* studies suggest that β -arrestin/ERK signalling is detrimental in asthma [9,10]. In this regard, propranolol, similar to carvedilol, activates β -arrestin/ERK signalling, while shutting down the Gs-cAMP pathway, while nadolol does the opposite. Thus, generalization of studies results simply regarding β -blockers as a "class" is not possible.

Ongoing basic and clinical research, including clinical trials regarding specific β -blockers will add compelling data to our knowledge on these drugs effects in obstructive pulmonary diseases. While data supporting longer-term safety is still lacking for patients with concomitant pulmonary and cardiovascular diseases, current evidence supports that asthma or COPD is not a contraindication for cardioselective β -blockers therapy. These patients should not be denied a therapy that markedly reduces cardiovascular symptoms and mortality. Low dose initiation and gradual up-titration of β -blockers is currently recommended. Thus, if indicated, cardioselective β -blockers should be prescribed in patients with asthma or COPD.

Authors' contributions

All authors have analysed the literature, wrote and edited the manuscript.

HP and MBC contributed equally to this manuscript.

Funding

None.

References

- [1] Morales DR, Jackson C, Lipworth BJ, et al. Adverse respiratory effect of acute beta-blocker exposure in asthma: a systematic review and meta-analysis of randomized controlled trials. *Chest* 2014;145:779–86.
- [2] Salpeter S, Ormiston T, Salpeter E. Cardioselective beta-blockers for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2005, CD003566.
- [3] Salpeter SR, Ormiston TM, Salpeter EE. Cardioselective beta-blockers in patients with reactive airway disease: a meta-analysis. *Ann Intern Med* 2002;137:715–25.
- [4] Hanania NA, Singh S, El-Wali R, et al. The safety and effects of the beta-blocker, nadolol, in mild asthma: an open-label pilot study. *Pulm Pharmacol Ther* 2008;21:134–41.
- [5] Short PM, Lipworth SI, Elder DH, et al. Effect of beta blockers in treatment of chronic obstructive pulmonary disease: a retrospective cohort study. *BMJ* 2011;342:d2549.
- [6] Du Q, Sun Y, Ding N, et al. Beta-blockers reduced the risk of mortality and exacerbation in patients with COPD: a meta-analysis of observational studies. *PLoS One* 2014; 9, e113048.
- [7] Lipworth BJ, Williamson PA. Beta blockers for asthma: a double-edged sword. *Lancet* 2009;373:104–5.
- [8] Short PM, Williamson PA, Anderson WJ, et al. Randomized placebo-controlled trial to evaluate chronic dosing effects of propranolol in asthma. *Am J Respir Crit Care Med* 2013;187:1308–14.
- [9] Bond RA. The intrinsic bias of generalizations. *Am J Respir Crit Care Med* 2014;189:359.
- [10] Walker JK, Penn RB, Hanania NA, et al. New perspectives regarding beta(2)-adrenoceptor ligands in the treatment of asthma. *Br J Pharmacol* 2011;163:18–28.

Helena Pité¹

Allergy Center, CUF Descobertas Hospital and CUF Infante Santo Hospital,
Lisbon, Portugal
CEDOC, Chronic Diseases Research Center, NOVA Medical School, Faculdade
de Ciências Médicas, Universidade Nova de Lisboa, Lisbon, Portugal
Corresponding author at: Allergy Center, CUF-Descobertas Hospital, Rua
Mário Botas, 1998-018 Lisbon, Portugal. Tel.: +351 962790162;
fax: +351 210025220.
E-mail address: helenampite@gmail.com.

Marisa Braga da Cruz¹

Allergy Center, CUF Descobertas Hospital and CUF Infante Santo Hospital,
Lisbon, Portugal

Mário Morais-Almeida

Allergy Center, CUF Descobertas Hospital and CUF Infante Santo Hospital,
Lisbon, Portugal
CINTESIS, Center for Research in Health Technologies and Information
Systems, Porto, Portugal

20 April 2016

Available online xxxx

¹ These authors contributed equally to this manuscript.