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Cardioselective beta-blockers for chronic obstructive pulmonary disease: a meta-analysis

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Summary Beta-blocker therapy has a mortality benefit in patients with hypertension, heart failure and coronary artery disease, as well as during the perioperative period. These drugs have traditionally been considered contraindicated in patients with chronic obstructive pulmonary disease (COPD). The objective of this study was to assess the effect of cardioselective beta-blockers on respiratory function of patients with COPD. Comprehensive searches were performed of the EMBASE, MEDLINE and CINAHL databases from 1966 to May 2001, and identified articles and related reviews were scanned. Randomised, blinded, controlled trials that studied the effects of cardioselective beta-blockers on the forced expiratory volume in 1 s (FEV1) or symptoms in patients with COPD were included in the analysis. Interventions studied were the administration of beta-blocker, given either as a single dose or for longer duration, and the use of beta2-agonist given after the study drug. Outcomes measured were the change in FEV1 from baseline and the number of patients with respiratory symptoms. Eleven studies of single-dose treatment and 8 of continued treatment were included. Cardioselective beta-blockers produced no significant change in FEV1 or respiratory symptoms compared to placebo, given as a single dose (−2.05% [95% CI, −6.05% to 1.96%]) or for longer duration (−2.55% [CI, −5.94% to 0.84]), and did not significantly affect the FEV1 treatment response to beta2-agonists. Subgroup analyses revealed no significant change in results for those participants with severe chronic airways obstruction or for those with a reversible obstructive component. In conclusion, cardioselective beta-blockers given to patients with COPD do not produce a significant reduction in airway function or increase the incidence of COPD exacerbations. Given their demonstrated benefit in conditions such as heart failure, coronary artery disease and hypertension, cardioselective beta-blockers should be considered for patients with COPD.

Introduction

Beta-adrenergic blocking agents, or beta-blockers, are indicated in the management of angina pectoris, myocardial infarction, hypertension, congestive heart failure, cardiac arrhythmia and thyrotoxicosis, as well as to reduce complications

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in the perioperative period.[1–14] Despite clear evidence of their effectiveness and mortality benefit, clinicians are often hesitant to administer them in the presence of a variety of common conditions for fear of adverse reactions.[15–18] Many patients with chronic obstructive pulmonary disease (COPD) have concomitant conditions such as angina or cardiac arrhythmias necessitating the use of beta-blockers. However, review articles and practice guidelines usually list asthma and COPD as contraindications to beta-blocker use, citing cases of acute bronchospasm occurring during non-cardioselective beta-blocker use.[6,8,19–23] Cardioselective beta-blockers, or beta1-blockers, have over 20 times more affinity for beta1 receptors as for beta2 receptors, and theoretically should have significantly less risk for bronchoconstriction.[24]

A recent meta-analysis demonstrated that beta1-blockers, given to patients with mild to moderate reversible airway disease, do not produce clinically significant adverse respiratory effects.[25] The study was not designed to make recommendations about people with significant chronic airway obstruction because only a few COPD patients met the reversibility criteria for the study. Patients with COPD are at greater risk of ischemic heart disease than asthmatics, so would benefit from the use of beta-blockers. However, they also have more severe airways obstruction, so may be more sensitive to small changes in FEV1 due to beta-blockade.

The objective of this review was to evaluate the effect of cardioselective beta1-blockers on respiratory function in patients with COPD, as assessed by forced expiratory volume in 1 s (FEV1) and the incidence of symptoms. Another objective was to evaluate the FEV1 response to beta2-agonists for those patients treated with beta1-blockers as compared to placebo. This analysis has already been published as a review on the Cochrane Library.[26]

Methods

Search strategy

A search was performed to identify all relevant published clinical trials that address the effects of cardioselective beta-blockers on airway function in patients with COPD. A comprehensive search of EMBASE, MEDLINE and CINAHL was performed to identify all relevant human clinical trials published between 1966 and May 2001. Terms used in the search were asthma*, bronchial hyperreactivity*, respiratory sounds*, wheez*, obstructive lung disease*, or obstructive airway disease*, and adrenergic antagonist*, sympatholytic* or adrenergic receptor block*. Trials were not excluded on the basis of language. The search was further augmented by scanning references of identified articles or reviews, and of abstracts at clinical symposia.

Study selection

Two investigators independently evaluated studies for inclusion and the observed percentage agreement between raters was calculated. Trials were included if they: (1) reported FEV1 measured at rest, either as litres or as a percent of the normal predicted value at baseline and follow-up, or reported symptoms for study drug and placebo, (2) were randomised, controlled, and single or double-blinded, and (3) included only subjects with COPD, demonstrated by a baseline FEV1 of $<80\%$ normal predicted value, or as defined by the guidelines of the American Thoracic Society.[27] Cross-over trials were considered to be randomised if different interventions were administered in random order. Controlled trials were those with placebo or comparative controls.

The decision was made to evaluate only beta1-blockers in this study as these are the ones most frequently used in clinical practice. Studies were included only if participants had documented COPD, in order to evaluate the effect of beta1-blockers in patients with chronic airway obstruction. Participants were not included or excluded on the basis of reversibility of their airway obstruction. Only blinded studies were included in order to decrease the risk of reporting bias that is inherent in unblinded studies. It was decided, a priori, that comparative trials studying FEV1 treatment effects of beta1-blockers without placebo controls would be included as long as they compared various interventions in a blinded randomised manner. The results of the trials without placebo controls were evaluated separately. For studies that evaluated symptoms, only those that have placebo controls for comparison to active treatment were included.

Assessment of validity

The methodological quality of each trial was assessed, using the following factors. (1) Was the study randomised? If so, was the randomisation procedure adequate? (2) Was the trial placebo-controlled? (3) Were the patients and people administering the treatment blind to the

intervention? (4) Were withdrawals and drop-outs described?

Study characteristics

The main intervention studied was the use of intravenous or oral beta1-blockers versus placebo or other interventions, given either as a single dose or for an extended period. A second intervention studied was the administration of a beta2-agonist, either intravenously or by inhalation, given after the study medication or placebo. For single-dose trials the beta2-agonist was given 1 h after the administration of an intravenous agent, and 3–6 h after an oral agent was given.

Data extraction

Two independent reviewers extracted data from the selected articles, reconciling differences by consensus. Outcomes measured were: (1) the change in FEV1 from baseline in response to study group or placebo, (2) FEV1 response to beta2-agonist administered after placebo or study drug, and (3) reported symptoms during the trial, such as wheezing, dyspnea, COPD exacerbation or hospitalisation, for study drug or placebo.

Respiratory symptoms were measured according to a self-reporting system used for each trial, and were reported as the number of patients with symptoms. For single-dose trials respiratory symptoms were described as wheezing, dyspnea or breathlessness. For trials of longer duration patients were to record symptoms such as acute shortness of breath, increased respiratory symptoms, asthma attacks or COPD exacerbations.

Data synthesis

To estimate the net treatment effect, the ratio of the lowest measured FEV1 value seen after study drug to baseline FEV1 were measured for both placebo and active treatment, and recorded as the percent change from baseline. The treatment response was then compared to the placebo response. For those studies without placebo controls the treatment response for each intervention was measured and the placebo response was estimated from the available placebo-controlled trials. The results from these trials are reported separately.

For those trials that did not provide information on the standard deviation (SD) for the study results, the average SD was obtained from trials that provided such data, calculated separately for placebo and treatment responses. This pooled SD was used for all trials that did not provide SD data. A sensitivity analysis was performed to evaluate the effect of including these trials.

The mean treatment effects were then pooled to get a weighted average of the study means using a fixed-effects model for continuous outcomes.[28,29] Confidence intervals (CI) with 95% significance were obtained for the pooled study means. In order to test for heterogeneity between studies, the chi-squared was calculated for the assumption of homogeneity.

In order to evaluate the response to beta2-agonist given after active treatment or placebo, the new baseline used was the FEV1 taken after study drug but prior to beta-agonist. The net treatment effect was estimated by calculating the ratio of FEV1 measured after agonist to the new baseline for both placebo and active treatment, and then comparing the treatment-agonist response to the placebo-agonist response.

Results for respiratory symptoms were measured as a risk difference, by subtracting the fraction of participants in the placebo group with symptoms from the fraction of those in the treatment group with symptoms. For cross-over trials each participant was counted only once, even if they received more than one treatment. It was planned to pool the risk differences for respiratory symptoms using the fixed effects model for dichotomous outcomes. However, as there were very few participants with increased respiratory symptoms, Poisson statistics was used, separately for treatment and placebo, in order to derive a CI for the pooled risk difference.

A subgroup analysis was performed to evaluate the response of patients with severe COPD, as defined by a mean baseline FEV1, for the group, of less than 1.4 l or less than 50% normal predicted value. Another subgroup analysis evaluated the treatment response of participants known to have reversible airway obstruction, documented by an increase in FEV1 of at least 15% to beta-agonist stimulation. A third analysis evaluated the response for those known to have comorbid cardiovascular conditions such as hypertension or angina. Trials without placebo controls were evaluated separately.

Results

Search results

The database search identified 200 potentially relevant articles. After review of the articles and bibliographies, 39 trials of beta-blockers in patients

with COPD were found. Of these, 19 met inclusion criteria: 11 gave information on single-dose studies,[30–40] and 8 provided data on treatment of longer duration.[41–48] Inter-rater agreement for study eligibility was 92%, and consensus was reached on the remaining 3 trials. Two of the single-dose trials did not provide baseline controls, and the results of these trials were reported separately.[35,39] Cardioselective beta1-blockers included in the studies were atenolol, metoprolol, bisoprolol, practolol, celiprolol and acebutolol.

Trials were excluded for the following reasons: 8 trials evaluated nonselective beta-blockers only, 2 studies were not randomised, 4 were not blinded, 1 did not provide FEV1 data or placebo controls, and 4 were reviews of other trials.

Methodological quality of included studies

All of the studies evaluated were small cross-over trials that included a wash-out period between treatment groups, and some of the trials were single-blind instead of double-blind. Two of the trials did not have placebo controls, and 1 study merely evaluated different doses of a single drug compared to baseline controls. The results of these trials are reported separately. In addition, many trials did not provide individual study SDs for the FEV1 treatment effect, and sensitivity analysis were performed to evaluate the effect of including these trials. The drop-out rate was 1.5% for single-dose studies and 3.5% for those of longer duration.

Quantitative data synthesis

Single-dose treatment results

Eleven studies on single-dose treatment included 141 participants, 80% of whom were men. There was an average of 12.8 patients per study, and the drop-out rate was 1.5%. From the available information the mean age of participants was 53.8 ($\pm$11.1) years. These baseline characteristics were the same for the placebo and treatment groups because all of the trials were cross-over by design. The baseline FEV1 measured in the treatment group was 1.64 ($\pm$0.63) l, and in the placebo group was 1.66 ($\pm$0.64) l.

Single doses of beta1-blockers were not associated with a change in FEV1 compared to placebo (−2.05% [CI, −6.05 to 1.96, Fig. 1]). The results were similar for those trials without placebo controls (−2.14% [CI, −7.32 to 3.04]). No participants had increased

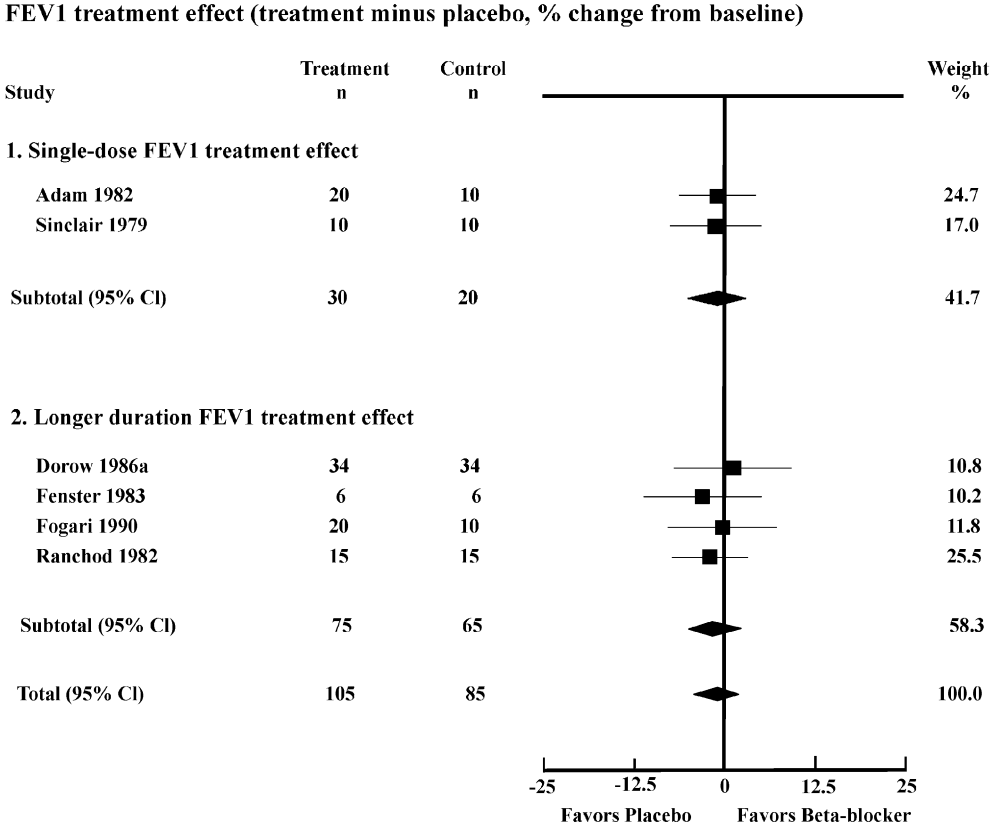

Figure 1 FEV1 treatment effects for single-dose and continued treatment studies.

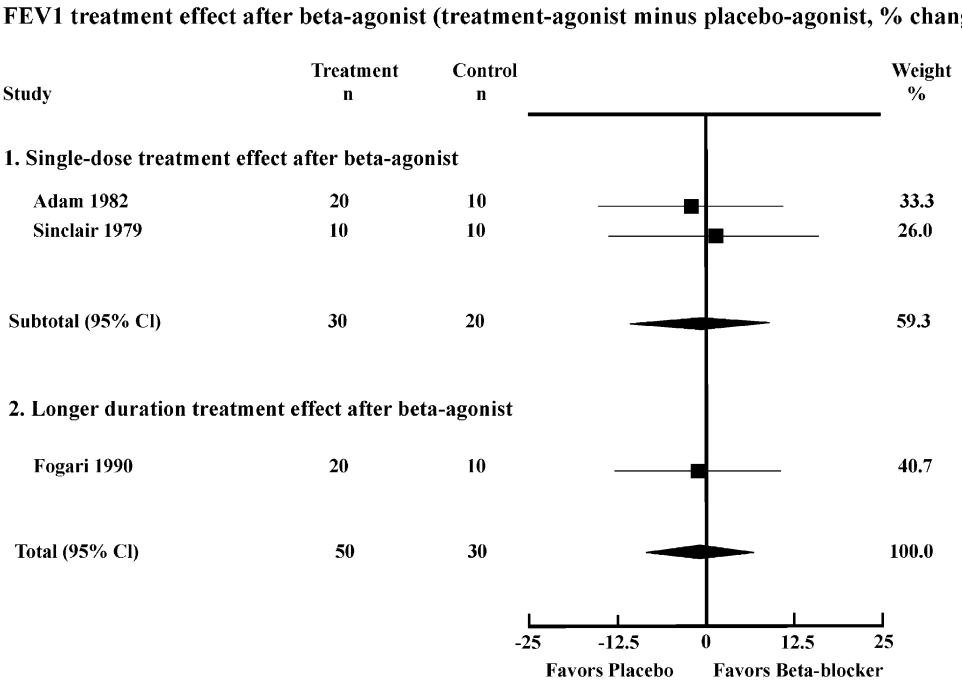

Figure 2 FEV1 treatment effects after beta2-agonists for single-dose and continued treatment studies.

respiratory symptoms with beta1-blockers or with placebo in any of the trials, with a risk difference (RD) of 0.0 (CI, −0.03 to 0.03). There was no significant change in the FEV1 treatment effect after beta2-agonist was given (−1.21% [CI, −10.97 to 8.56, Fig. 2]).

Longer duration treatment results

Data from 8 studies involving 126 participants (20.4 patient-years) were evaluated for treatment effects of longer duration ranging from 2 days to 3 months, with a mean trial duration of 1.1 months. There was an average of 15.8 participants in each study (77% of whom were men), with a 3.5% drop-out rate. The average baseline FEV1 in the treatment group was 1.74 (±0.76) l, and for the placebo group was 1.73 (±0.77) l.

In the continued treatment trials, beta1-blockers as a group did not significantly differ from placebo in terms of FEV1 response (−2.55% [CI, −5.94 to 0.84, Fig. 1]), number of patients with symptoms (RD 0.0 [CI, -0.04 to 0.04]), or response to beta2-agonists (−2.0% [CI, −13.77 to 9.77, Fig. 2]).

Interstudy variance

There was minimal interstudy variance in the measurement of FEV1 for single-dose studies ($P = 0.62$) and for studies of longer duration ($P = 0.4$). No evidence of interstudy heterogeneity was seen for respiratory symptoms, for single-dose studies ($P = 1$) or for those with longer duration ($P = 0.98$).

Subgroup analyses

To evaluate the effect of treatment in patients with severe chronic airways obstruction, 6 trials that demonstrated an average baseline FEV1 of <1.4 l or <50% normal predicted values were analysed separately.[35,38,41,43,44,48] There was no significant difference in FEV1 treatment effect for the single-dose studies (−2.4% [CI, −8.67 to 3.87]) or for those with continued treatment (−3.11% [CI, −8.62 to 2.41]), and no increase in symptoms was seen in any of the trials.

Another subgroup analysis concerned patients who had COPD with a reversible component as demonstrated by an improvement in FEV1 of at least 15% after beta2-agonists.[30,33,34,40,42–44] When these 7 trials were analysed separately, there still was no significant change in FEV1 seen in single-dose trials (−1.8% [CI, −7.01 to 3.41]) or those of longer duration (−1.26% [CI, −5.78 to 3.25]), and no increase in symptoms were found in any study.

In 8 of the trials, all participants had comorbid cardiovascular conditions such as hypertension or angina.[30,31,34,36,40,46–48] When only these trials were included in the analysis, there was no significant FEV1 treatment effect seen for single-dose studies (−1.8% [CI, −7.01 to 3.41]) or for those of longer duration (−4.20% [CI, −9.32

to 0.92]), and no respiratory symptoms were seen in the treatment group in any of the studies.

Sensitivity analyses

A sensitivity analysis was performed to evaluate the effect of including trials that did not provide study SDs for the FEV1 treatment effect.[35,38,43,44,46] Excluding trials that did not provide SD data did not significantly effect the results for single-dose trials (−3.01% [CI, −7.12 to 1.09]), or for those of longer duration (2.5% [CI, −5.38 to 10.38]).

Comment

This meta-analysis demonstrates that cardioselective beta-blockers in patients with COPD produced no significant change in FEV1 or respiratory symptoms compared to placebo, and did not affect the FEV1 treatment response to beta2-agonists. These findings were unchanged in subgroup analyses of patients with severe COPD or for those with a reversible obstructive component. These findings are supported by a recent meta-analysis that demonstrated that cardioselective beta-blockers given to patients with reversible airway disease did not produce clinically significant adverse respiratory effects.[25]

This meta-analysis has several limitations, some that are similar to those found with most meta-analyses.[49] The analysis only reports on published literature and is therefore subject to publication bias. However, funnel plots of effect size versus standard error for the trials in this review showed no evidence of bias. A few studies did not have placebo controls, and many did not provide standard deviations for FEV1 treatment effects. However, sensitivity analyses were performed to evaluate the effect of including these trials and the results were found to be consistent throughout, due to the homogeneous nature of the individual trials. Most of the studies were small and 80% of the participants were men. The participants were relatively young (mean age 54 years) with moderately reduced FEV1 (1.6 l). In addition, most of the studies were of short duration. It is possible that a longer study period may be required in order to detect clinically important side-effects of beta-blockers.

The current standard of care is to avoid the use of beta-blockers in patients with reactive or obstructive airway disease.[6,19–23] This reluctance to use beta-blockers is based on case reports of acute bronchospasm in patients with reversible airway disease precipitated by high doses of non-cardioselective beta-blockers.[50–53] Only a small fraction of patients with heart disease who would benefit from beta-blockers are currently given this treatment.[54–57] A recent study showed that COPD and asthma were the co-morbidities most commonly associated with beta-blockers being withheld in elderly patients after a myocardial infarction.[58]

This meta-analysis indicates that the use of cardioselective beta-blockers is safe in patients who have COPD, even in a subgroup of patients with concomitant angina, ischemic heart disease or hypertension. These findings are consistent with other studies that have shown that the use of beta-blockers in patients with COPD and concomitant cardiovascular disease is well tolerated.[59–65] Another study on survivors of myocardial infarction included 46,000 patients with asthma or COPD, and showed a significant reduction in total mortality for those treated with beta-blockers compared to those who were not.[15]

The studies in this meta-analysis gave doses of beta1-blockers ranging from therapeutic to supra-therapeutic doses, those that are not generally used for initiation of treatment. For example, subjects were given single doses of metoprolol or atenolol ranging from 50 to 200 mg, without a clinically apparent effect on respiratory function. However, it would be reasonable in clinical practice to start treatment with a low daily dose of a beta1-blocker, such as 25 mg of atenolol, and titrate the dose up as needed.

Due to the proven mortality benefit of beta-blockers in numerous conditions, many of the other relative or absolute contraindications traditionally listed for beta-blockers have been questioned and disproved, including impaired left ventricular function, peripheral vascular disease, diabetes mellitus, depression, and advanced age.[11,15,66–74] This meta-analysis suggests that cardioselective beta-blockers may be given to patients with COPD, even in those with a reversible component or with severe baseline obstruction.

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