Inhaled medication other than antibiotics

Inhaled bronchodilators

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Background

Inhaled bronchodilators (IBs) comprise two main classes: anticholinergics (ACs) and ??-agonists (BAs). Despite differing mechanisms of action, both promote relaxation of bronchial smooth muscle. Each class includes short- and long-acting agents that can be delivered via dry powder inhalers, metered-dose inhalers, or nebulizers. Beyond bronchodilation, ACs may reduce mucus secretion, whereas BAs can increase it; BAs also enhance mucociliary clearance and may help protect the bronchial mucosa from bacterial injury.

In advanced lung disease, IBs may paradoxically worsen airway function, potentially inducing bronchoconstriction due to abnormal airway compliance associated with bronchiectasis.

IBs are widely used in obstructive lung diseases other than cystic fibrosis (CF), including COPD, asthma, and bronchiectasis. In these conditions, combination therapy with long-acting ACs and BAs has been proposed as beneficial (Tashkin DP, 2013).

In CF, short-term IB use is recommended to relieve bronchospasm-related symptoms and to prevent adverse events during nebulized therapies (Mogayzel PJ, 2013). However, in the absence of documented reversible airway obstruction, recommendations for bronchodilator use remain inconsistent (Levine H, 2016), reflecting limited evidence for sustained improvements in lung function (Barry PJ, 2017).

More recently, Kieninger et al. (2022) suggested—based on novel diagnostic modalities such as multiple-breath washout and MRI—that IBs may produce short-term improvements in FEV? independent of ventilation inhomogeneity. Nonetheless, the marked inter-individual variability in response indicates that bronchodilator therapy should be assessed on a case-by-case basis.

Issues

IB efficacy in CF lung disease (lung function, respiratory symptoms, quality of life, pulmonary exacerbation rates, mortality rates)

IB adverse effects (tremor, increased heart rate, dry mouth, increased wheeze, and shortness of breath)

What is known

A 2016 Cochrane Review (Halfhide C, 2016) analyzed 18 randomized controlled trials involving 369 participants (children and adults). Overall, beneficial effects were observed, particularly in patients demonstrating bronchodilator responsiveness or bronchial hyperreactivity. No significant adverse events were reported, even with long-term use. The evidence supporting ??-agonists (BAs) appeared stronger than that for anticholinergics (ACs).

In 2016, this review was withdrawed because divided into two further Cochrane Reviews: *Long-acting inhaled bronchodilators for cystic fibrosis* and *Short-acting inhaled bronchodilators for cystic fibrosis*. The former, updated in December 2017 (Smith S, 2017), included three trials assessing both short-term (up to 28 days) and longer-term (up to three months) outcomes in 1,066 individuals with cystic fibrosis. The authors found no significant differences between intervention and placebo groups in quality of life, adverse events, or spirometric measures. Overall, evidence supporting the long-term effects of inhaled bronchodilators (IBs) remains limited, particularly given their potential impact on mucus production and mucociliary clearance. Further investigation is warranted into combinations of BAs and ACs, as well as the use of IBs alongside inhaled corticosteroids and other mucoactive therapies.

In 2022, a Cochrane Review on short-acting inhaled bronchodilators for cystic fibrosis was published (Smith S, 2022). This review included 11 trials with a total of 191 participants. All studies were small, employed crossover designs, and did not assess long-term outcomes. Consequently, the overall quality of evidence across all outcomes was judged to be very low.

A 2017 study (Furlan LL, 2017) further highlighted the potential role of the rs4073 polymorphism in the interleukin-8 gene in modulating the response to inhaled bronchodilators.

Unresolved questions

IB efficacy in CF lung disease (lung function, respiratory symptoms, quality of life, pulmonary exacerbation rates, mortality rates)

IB adverse effects (tremor, increased heart rate, dry mouth, increased wheeze, and shortness of breath)

No RCT are ongoing about this issue.

A recent paper by Garcia et al (Garcia AMG, 2026) bring into question the frequent use of IB (and of inhaled steroids - ICS) in CF. The authors consider that it is not easy to determine the true reasons behind the overutilization of bronchodilators and ICS in patients with bronchiectasis and CF worldwide, despite a clear lack of scientific evidence and official recommendations against their use beyond the coexistence of asthma or COPD. Clinicians should re-evaluate the need for bronchodilators and/or ICS, and rather than merely continuing the medications they should query whether their continuance is justified. Or, when starting one (or both) of these medications, they should clearly define the intent and expected outcomes, and consider stopping them after a trial if those expectations are not achieved. The authors acknowledge that the guidelines based their recommendations on limited evidence. Although it is likely that some patients will benefit from the use of these medications, it is equally likely that many patients are prescribed them unnecessarily adding cost, burden, and potential adverse effects. Greater efforts should be made to determine the true necessity of these medications in each patient and consideration for withdrawal from patients currently using them. Although it is unlikely there will be studies evaluating bronchodilators or ICS in bronchiectasis or CF in the near term given competing priorities, there remains a need for pragmatic trials of de-prescribing in these patients. Indeed, a blinded, controlled study of ICS withdrawal in CF and bronchiectasis patients resulted in no adverse outcomes.

Keywords

Adrenergic beta-Agonists; Anticholinergic Agents; Bronchodilator Agents; Xanthines;