Clinical effects of long-acting β2-agonists in methacholine-induced bronchoconstriction
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Summary

Asthma is a chronic airway disease characterised by chronic airway inflammation and periods of bronchoconstriction. Symptoms of asthma are dyspnoea, cough, chest pain, fatigue etc. The disease has different stages, depending on the severity, frequency of symptoms, and objective measurements. The pharmacological treatment of asthma is based on the severity of the disease. Long-acting β2-agonists formoterol and salmeterol should be considered when symptoms are moderately persistent and nightly symptoms occur. They provide an excellent bronchodilating effect, but there are differences between these compounds. In chapter 2, the state of the art of the current knowledge of the long-acting β2 agonists is discussed. Formoterol and salmeterol differ in rate of onset of the bronchodilating effect. Previously, it was demonstrated that formoterol provided a faster improvement in lung function (FEV\textsubscript{1}) than salmeterol after inducing an acute, methacholine-induced moderate to severe bronchoconstriction. In chapter 3, we demonstrate that formoterol also provides a rapid subjective improvement of dyspnoea, similar to that of salbutamol and faster than salmeterol.

A further important difference between formoterol and salmeterol in vitro, is the full agonistic property (higher intrinsic activity) of formoterol in comparison to the partial agonist salmeterol. In the subsequent two chapters (chapters 4 and 5) we tried to demonstrate this difference in vivo, using methacholine-induced bronchoconstriction as a model, by studying (chapter 4) the bronchodilating effect of an additional single dose of salbutamol. The hypothesis was that after pretreatment with a high dose of salmeterol, the bronchodilating effect of salbutamol would be decreased, in contrast to high dose treatment with formoterol. However, at the investigated dose of salbutamol, no difference in the bronchodilating effect could be demonstrated. In fact, due to the two-week pretreatment period, the bronchodilating effect of salbutamol was diminished to a similar extent with both long-acting β2-agonists, indicating the development of tolerance, overshadowing the putative occurrence of antagonistic activity of salmeterol. Nevertheless, after formoterol pretreatment, a higher dose of methacholine was needed to induce a similar bronchoconstriction, confirming in vitro data that formoterol has a greater intrinsic activity than salmeterol.

In chapter 5, a different approach was chosen by studying the acute effects of salmeterol and formoterol treatment on the bronchodilatory dose response curve of formoterol, performed on top of a methacholine-induced bronchoconstriction. Remarkably, also in this study the bronchodilating effects of formoterol were not differently modulated by pretreatment with salmeterol compared to formoterol.

With the introduction of the long-acting β2-agonists there were two major concerns: blunting of perception of dyspnoea and decrease of compliance with inhaled corticosteroids (ICS). As outlined in the introduction of this thesis, the perception of
dyspnoea is an important feature for the asthmatic patient and a cornerstone in the treatment of asthma. Using the modified Borg scale, we showed in chapter 6 that a methacholine-induced moderate to severe bronchoconstriction was well perceived after two weeks of high dose treatment of long-acting β₂-agonists; no differences were observed between formoterol, salmeterol, and placebo pretreatment. The first concern appeared therefore to be unjustified. Another concern was that with the start of the (subjectively) strong-acting long-acting β₂-agonists the compliance with ICS might decrease. ICS do not have an immediate bronchodilating effect and many patients rate them as ineffective. In chapter 9, we showed that no decrease in compliance with ICS was observed, when long-acting β₂-agonists were added in patients who chronically use ICS. On the contrary, this study shows that the addition of long-acting β₂-agonists may improve compliance.

Guidelines recommend that long-acting β₂-agonists should always be combined with ICS. Until recently, these medications were only available in separate inhalers. At present, these medications are available in a single inhaler, like Seretide® (fluticasone/salmeterol) and Symbicort® (budesonide/formoterol). Combination inhalers that combine long-acting β₂-agonist with ICS may facilitate asthma treatment by reducing the number of inhalations and inhalators and therefore have the potential to improve the compliance and consequently asthma control. With the availability of these new combination products, patients could be tempted to use them in a situation of acute bronchoconstriction. In chapter 7, Symbicort® reverses a methacholine-induced bronchoconstriction rapidly, both objectively by means in improvement in FEV₁ and subjectively by means of improvement in Borg score. The fast onset of bronchodilatory effect was comparable with formoterol and salbutamol in a similar model and even a lower dose of formoterol (6 µg) provided a similar fast onset of action. From that study it remains unclear whether the corticosteroid component of the combination contributed to the fast onset of effect. The results suggest, however, that Symbicort® has potential to be used as needed.

Long-acting β₂-agonists are not only used in patients with asthma, but also in patients with COPD. Many patients with COPD have cardiovascular comorbidity and therefore are β₂-agonists often needed. Whereas β₂-agonists stimulate the receptor, β₁-antagonists block the receptor. In the study described in chapter 8, formoterol showed a rapid onset of action in reversing a methacholine-induced bronchoconstriction in COPD-patients irreversible to salbutamol, but its effectiveness was hampered by β₂-receptor blockade. This warrants the use of non-selective β-adrenergic antagonists or higher doses of cardioselective β₁-adrenergic antagonists. Remarkably, lipophilic β₁-selective and non-selective antagonists were found to deteriorate airway hyperresponsiveness in these patients with mild to moderate COPD and irreversible airway obstruction. They may also have a negative effect on lung function (FEV₁). These results may have important bearings on the management of COPD patients, especially since cardiovascular comorbidity is frequently present. Further studies have to elucidate whether these observations also hold for COPD, especially with cardiovascular comorbidity. Given the increasing burden of COPD, these combination products may help to improve the consequences of airway obstruction by potentiating the bronchodilatory effect of β₂-agonists combined with the anti-inflammatory effect of ICS. Further studies need to be addressed to elucidate whether these combination products may have an advantageous effect on lung function.
hold for patients with more severe COPD. In elderly patients with suspicion of COPD, we recommend lung function measurements before β-antagonists are being prescribed.

**Conclusions**
- rapid acting β₂-agonists provide a rapid (objective and subjective) improvement of dyspnoea.
- formoterol shows also in vivo a higher intrinsic activity than salmeterol.
- antagonistic properties of the partial agonist salmeterol do not readily occur in vivo.
- formoterol does not cause a stronger tolerance than salmeterol.
- long-acting β-agonists do not deteriorate the perception of dyspnoea.
- the combination of budesonide and formoterol in a single inhaler provides a rapid, subjective and objective, improvement of dyspnoea.
- in COPD, β-blockers may deteriorate airway hyperresponsiveness not only because of β₂-receptor blockade.
- formoterol is effective in reversing a methacholine-induced bronchoconstriction in patients with irreversible COPD, but its effectiveness can be compromised by β₂-receptor blockade.
- the addition of long-acting β-agonists to inhaled corticosteroids improve the compliance with inhaled corticosteroids.