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PERSPECTIVE

Do long-acting β_2-adrenergic agonists deserve a different place in guidelines for the treatment of asthma and COPD?

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The introduction of long-acting β_2-adrenergic agonists (salmeterol and formoterol) in the early 1990s came at a rather critical moment. Various epidemiological studies had recently demonstrated a relationship between prolonged use of β_2-adrenergic agonists and mortality due to asthma [1–5]. These publications did not go unheeded: they triggered intense debate on the possible risks of the use of β_2-agonists. One of the main criticisms that these studies elicited was that they did not provide any hard evidence for a cause/effect relationship. In other words, it could not be deduced from these studies that prolonged use of β_2-agonists (fenoterol in particular) was the true cause of increased mortality due to asthma. Severe asthma is accompanied by not only higher mortality but also frequent use of β_2-agonists. The connection between prescription of these agonists and mortality could therefore also be reversed (so-called "confounding by indication"). A meta-analysis based on the most important epidemiological studies confirmed the suspicion that there indeed existed a reverse relationship [6]. However, as meta-analysis of such patient/control studies always has a number of methodological limitations, there was a clear need for randomized prospective studies.

In 1990/1991, two randomized longitudinal intervention studies were published, in which prolonged use of β_2-agonists seemed to be the cause of diminished control over asthma [7] and a relatively rapid decline in lung function [8]. Partly because of this, there was growing concern regarding the possible harmful effects of prolonged use of these drugs. Although these findings were not supported by other studies [9–12], physicians (and patients) had the feeling that the recently introduced long-acting β_2-agonists should be used with due caution. Further studies were therefore required. It turned out that prolonged use of not only short-acting β_2-agonists, but also a long-acting agonist led to a decrease in the protective effects against bronchoconstrictive stimuli in the long term [13, 14]. However, this was not accompanied by an increase in bronchial hyperresponsiveness or a diminished bronchodilatory effect of these long-acting drugs [14, 15]. Although, at first sight, this last aspect seems positive, it simultaneously reinforces the idea that these very effective bronchodilators may mask the severity of the disease in the long run. After all, the long-acting β_2-adrenergic agonists have not been shown to have a broad anti-inflammatory effect. Significant exposure to irritants (*e.g.* allergens or smoke) might unexpectedly cause a serious obstruction, with the patient not noticing any deterioration in their condition at the time, because all symptoms are suppressed so effectively by these long-acting drugs. Moreover, there is a risk that the absence of symptoms will lead to less compliance with regard to inhaled corticosteroids, which have just the anti-inflammatory effect that β_2-agonists do not have.

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The place of long-acting β_2-adrenergic agonists in the treatment of asthma

The above-mentioned considerations led to a situation in which, in all international guidelines, long-acting β_2-agonists are reserved for moderate-to-severe chronic asthma and always and exclusively prescribed in combination with inhaled corticosteroids [16–17]. In practice, this means that long-acting agonists are only prescribed when short-acting agonists and inhaled corticosteroids (the latter at a dose of 400–800 μg daily) do not produce sufficient effect. In such cases, it is advisable to further increase the dose of inhaled corticosteroids or add long-acting β_2-agonists (fig. 1).

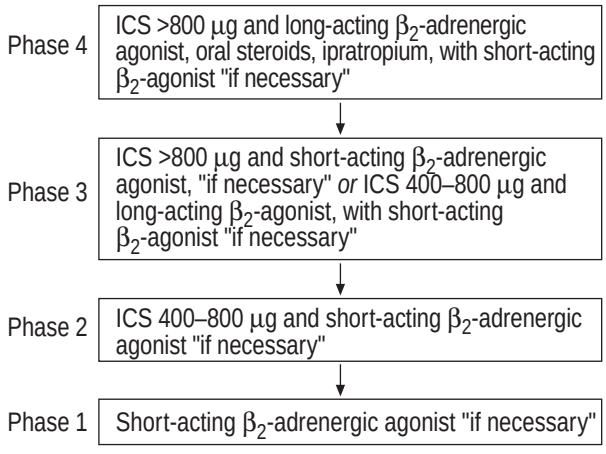

Fig. 1. – Current phased plan (simplified) for the treatment of asthma based on Global Initiative for Asthma guidelines [16]. The arrows indicate that the medication can be gradually decreased, if possible. Phase 4: severe persistent asthma; phase 3: moderate persistent asthma; phase 2: mild persistent asthma; phase 1: intermittent asthma. ICS: inhaled corticosteroids.

As patients seem to benefit considerably from long-acting β_2-agonists and these can be used quite simply twice a day, the option to let these drugs play a more central role in the treatment of asthma is certainly attractive. It is then, of course, important that this will not lead to the risks already mentioned.

To further examine the place of long-acting β_2-agonists in the treatment of asthma (see the phased plan in figure 1), large-scale and well-controlled international studies have been carried out over the past few years [18–20]. The combination of a long-acting β_2-adrenergic agonist (salmeterol 100 μg daily) and an inhaled corticosteroid (beclomethasone 400 μg daily) was compared with a higher dose of the steroid (1,000 μg daily) alone [18]. Peak flow improved and symptoms decreased when the combination of steroid and long-acting β_2-agonist was used. In another trial involving patients with more severe asthma who could not be treated effectively with 1,000 μg inhaled corticosteroids daily alone, two different combinations of a long-acting β_2-agonist and inhaled corticosteroid (salmeterol 100 μg and beclomethasone 1,000 μg daily *versus* salmeterol 200 μg and beclomethasone 1,000 μg daily) were compared with a high dose of the inhaled corticosteroid (2,000 μg daily) alone [19]. Again, addition of the long-acting β_2-agonist clearly proved to lead to a greater improvement in symptoms and peak flow than did the increased dose of inhaled corticosteroids on its own. The higher dosage of the long-acting agonist (salmeterol 200 *versus* 100 μg daily) did not prove to be of any additional value.

Although both trials were well set up, they might be criticized because they covered a period of only 6 months and because the primary outcome was evaluated on the basis of lung function and symptoms at a time when the long-acting agonists were still active to some extent. Thus, although symptoms may have decreased and lung function improved during the use of these drugs, there still remains a risk that these outcomes are masking possible underlying inflammatory processes or the increase thereof. When control of asthma is the primary aim of a study, it is particularly important to know whether or not exacerbations occur during the long-term use of these drugs. It was especially in view of this that the Formoterol and Corticosteroids Establishing Therapy (FACET) study was set up: a 12-month trial during which the effects of various doses of an inhaled corticosteroid (budesonide 200 *versus* 800 μg daily), possibly combined with a long-acting β_2-adrenergic agonist (formoterol 24 μg daily), were studied in 852 asthma patients [20]. Remarkably, the long-acting agonist did not only improve lung function and decrease symptoms but also reduced the number of mild and severe exacerbations (by 40 and 29% respectively). This was the case with not only the high dose of the inhaled corticosteroid (800 μg daily) but also the low dose (200 μg daily). This last observation is highly relevant, because this might imply that the addition of a long-acting β_2-agonist could be useful from the mild-persistent asthma stage (phase 2 in figure 1, in which a low dose of corticosteroids is administered). This might lead to long-acting agonists being introduced at a much earlier stage. Short-acting agonists might then be primarily reserved for intermittent asthma and the long-acting ones for persistent asthma. It should be stressed, however, that long-acting agonists should always be administered in combination with inhaled corticosteroids. The dose of steroids may be increased consistent with the severity of the asthma; the FACET study also shows that a higher dose of inhaled corticosteroids results in fewer exacerbations.

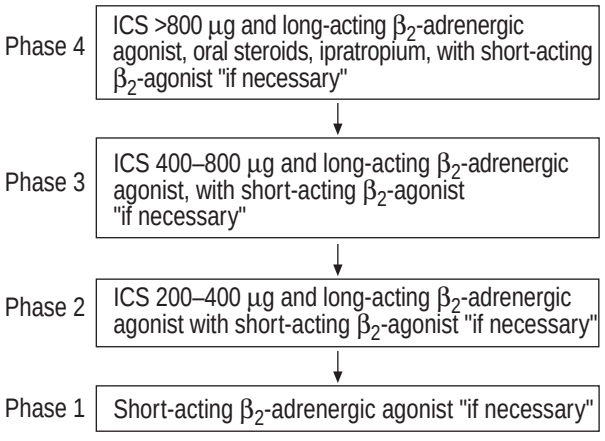

Fig. 2. – Example of a possible future phased plan for the treatment of asthma, based on new insights into the effects of long-acting β_2-adrenergic agonists. The arrows indicate that the medication can be gradually decreased, if possible. ICS: inhaled corticosteroids. Phase 4: severe persistent asthma; phase 3: moderate persistent asthma; phase 2: mild persistent asthma; phase 1: intermittent asthma.

Possible adaptation of the phased plan

The considerations mentioned above may lead in the long run, to adaptation of the phased plan (fig. 2). It should be emphasized that such adaptation cannot be carried out without first having obtained the results of well controlled trials conducted over a period >12 months. To prevent a decrease in compliance with regard to inhaled corticosteroids as a result of the efficacy of long-acting β_2-agonists, the administration of inhaled corticosteroids and long-acting β_2-agonists in a fixed combination might be considered. This may involve various dosages of the inhaled corticosteroid, depending on the severity of the asthma. Labelling these various dosages with various colours, for instance green, orange and red (comparable to the colours corresponding to the peak flow ranges in recent self-management plans), could be considered.

Recently, it has been suggested that, when a long acting β_2-agonist (formoterol) is used on demand, it also might improve quality of life and asthma control [21, 22]. However, this evidence is thus far not sufficient to propose the introduction of long-acting β_2-agonist even earlier than in phase 2.

The place of long-acting β_2-adrenergic agonists in the treatment of chronic obstructive pulmonary disease

In international guidelines, the place of long-acting β_2-adrenergic agonists in the treatment of chronic obstructive pulmonary disease (COPD) is much less clear than that in the treatment of asthma. In several guidelines for the treatment of COPD, the use of long-acting β_2-agonists is solely reserved for symptomatic treatment of nocturnal dyspnoea

[23]. The most important reason why the place of these agonists is not yet very clear is the lack of well-controlled randomized long-term trials. Compared with short-acting β_2-agonists and anticholinergics, the long-acting agonist has a notably stronger bronchodilatory effect in COPD 4–12 h after administration [24, 25]. The use of long-acting agonists may therefore have important advantages in COPD: they can be given twice daily and can also be used to prevent nocturnal dyspnoea (which is a major symptom in COPD). As in asthma, long-acting β_2-agonists decrease symptoms and improve peak flow in COPD [26]. Although the obstruction often seems irreversible (at least to a large extent) and therefore leaves little room for absolute improvement in the obstruction in COPD patients, the use of long-acting agonists has proved to produce a decrease in dyspnoea [27] and a clear improvement in quality of life [28]. There are indications that the change in lung function in COPD patients (measured as the forced expiratory volume in one second (FEV_1)) is less relevant than that in airway resistance and work of breathing. The latter two variables improve during use of a long-acting β_2-agonist without there being any evident improvement in the FEV_1 [29]. Moreover, it has been demonstrated that, after use of a long-acting agonist, the walking distance achieved during the 6-min walking test improved significantly, whereas there was no evident improvement in the FEV_1 [30]. The FEV_1 may therefore be a less suitable parameter for evaluating the effectiveness of bronchodilators in COPD. For COPD patients, the improvements in work of breathing, walking distance and quality of life are, of course, of great importance.

It is not yet clear what will be the place of long-acting anticholinergics for chronic obstructive pulmonary disease patients. Initial experience with long-acting tiotropium bromide in chronic obstructive pulmonary disease patients is promising [31, 32].

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