Indacaterol, A Novel Once Daily Inhaled β2-Adrenoreceptor Agonist

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Abstract: In this article we will review the role of long acting β2-adrenoreceptor agonists and long-acting muscarinic agents in the management of airflow obstruction. We will then focus our attention on indacaterol, one of the new once daily inhaled β2-adrenoreceptor agonists. Pharmacologically this drug is a nearly full β2-agonist without loss of efficacy after prolonged administration. We will also discuss its dosing, safety and tolerability.

Keywords: Indacaterol, tachyphylaxis, activity profile, safety.

ROLE OF LONG ACTING β2-ADRENORECEPTOR AGONISTS AND LONG-ACTING MUSCARINIC AGENTS IN THE MANAGEMENT OF AIRFLOW OBSTRUCTION

International guidelines on chronic obstructive pulmonary disease (COPD) and bronchial asthma [1, 2] underline the clinical benefit derived from including long acting bronchodilators in their therapeutic approach. The current gold standard therapy for treating patients with moderate-to-severe persistent asthma is the combination of a long acting β2-adrenoreceptor agonist (LABA) with an inhaled corticosteroid. Long acting β2-adrenoreceptor agonists (LABAs) have also a well established role in the treatment of stable COPD. It is well known that a simplified dosing regimen will improve patients’ compliance [3], a key point in multi-step therapeutic regimens such as those that are often prescribed to individuals with COPD or asthma. That is why long acting agents, particularly once-daily inhalers, will offer a better adherence than other drugs that require a more complicated dosing schedule.

LABAs are highly lipophilic compounds. This characteristic helps to prolong their duration of action since they dissociate more slowly than short-acting β2-agonists from lung fat-soluble tissues. Formoterol and salmeterol have been the LABAs usually prescribed by most clinicians during the last decades [4]. However, a few drugs have been developed for the last years to attempt to improve the therapeutic profile of these classical LABA. Ultra-LABA is the term used to describe a variety of new β2-adrenoreceptor agonists that have focused their action in a more prolonged half life with the aim of making feasible a one-day dose administration. Indacaterol (QAB-149), carmoterol (CHF-4226, TA-2005), GSK-159797, and GSK-642444 are some of these new ultra-LABAs that are still in different phases of clinical development [5, 6].

Parallel to what happens with β2-adrenoreceptor agonists new long acting antimuscarinic agents (LAMAs) are also under preclinical development in an attempt to improve some aspects of the excellent therapeutic profile that tiotropium has shown since this drug has become commercially available [7]. Aclidinium, NVA237, OrM3, and CHF 5407 are some of these new LAMAs which are also in different phases of preclinical development. The combination of a long acting β2-adrenoreceptor agonist (LABA) and a long-acting muscarinic agent (LAMA) is an innovative approach that will most likely be a significant therapeutic progress in a selected population of patients with airflow obstruction. However, further studies are clearly warranted before we can define which population of patients will really benefit from these future therapeutic combined agents.

This review focuses on indacaterol (QAB 149; Novartis, Basel, Switzerland) [8, 9], one of the new once daily inhaled β2-adrenoreceptor agonists that has completed phase II and phase III clinical trials for the treatment of asthma and COPD.

INDACATEROL: ACTIVITY PROFILE

Pharmacologically, indacaterol is a nearly full β2-agonist [10]. Tissue and experimental studies show longer durations of action for indacaterol when compared to salmeterol or formoterol, demonstrating sustained bronchodilator efficacy throughout the full 24-hour period [11, 12]. In a human lung slice model Sturton et al. [13] have demonstrated that indacaterol has a superior activity than salmeterol and a similar intrinsic efficacy to formoterol. Onset of action, with a fast acting action, is very similar for indacaterol and formoterol and slower for salmeterol. This experimental finding correlates well with what has been observed in initial clinical studies, since a statistically significant beneficial effect is demonstrated in those patients receiving indacaterol within the first 5 minutes after inhalation. A rapid onset of effect may increase patients’ confidence in treatment and subsequently improve therapy compliance. Opposite to this rapid absorption and onset of action for indacaterol, salmeterol
Improvement in FEV\textsubscript{1} occurs within 15 minutes after inhalation. Functional data show highest, about twofold, intrinsic activity for formoterol and indacaterol than for salbutamol or salmeterol [8].

**INDACATEROL: DOSING**

Rennard et al. [14] conducted a dose-ranging study, with a tiotropium comparison, to elucidate which dose of indacaterol shows 24-hour effectiveness in patients with moderate-to-severe COPD. Functional inclusion criteria were prebronchodilator FEV\textsubscript{1} ≥ 40% of predicted, FEV\textsubscript{1} ≥ 1.0 L, and FEV\textsubscript{1}/FVC < 70%. Six hundred thirty-five patients were eventually randomized to receive 50, 100, 200 or 400 μg or placebo once daily for 7 days. All indacaterol doses significantly increased FEV\textsubscript{1} from 5 minutes to 24 hours post-dose but 400 and 200 μg were the dose most effective. A subset of subjects from each treatment group entered an open label extension and received tiotropium 18 μg once daily for 8 days. Indacaterol through FEV\textsubscript{1} levels compared favorably with the improvement observed by day 8 in patients that received tiotropium in this subgroup of patients taking part in the open-label extension. Overall, a 400 μg dose was the most effective in this study.

Single 200 μg and 400 μg doses provide effective and sustained 24-hour bronchodilator control and a rapid onset of action (< 5 minutes) in asthmatic patients. A 200 μg dose seems to be the optimum dose regarding efficacy and safety balance. On another dose-ranging study designed to establish the optimal dose for indacaterol inhaled treatment in patients with persistent asthma, LaForce et al. [15] also reported that a 200 μg dose seems to offer the best efficacy/safety balance in most subjects.

**INDACATEROL: TACHYPHYLAXIS**

It has been stated that β\textsubscript{2} adrenoreceptor downregulation may follow chronic administration of LABAs in asthma. The consequence would be a subsequent reduced sensitivity, known as tachyphylaxis, of airway smooth muscle and inflammatory cells response. It must be emphasized that tachyphylaxis has not been observed with long-term indacaterol administration. Many studies have shown that there is no loss of efficacy with prolonged administration of indacaterol since sustained improvements on FEV\textsubscript{1} are consistently observed in those clinical trials that have addressed this issue. A low need of rescue medication in the indacaterol arm has also been occasionally highlighted in some comparative clinical trials of indacaterol and other LABAs.

**INDACATEROL: INTERACTION WITH SHORT ACTING β\textsubscript{2}-ADRENERGIC AGENTS (SABAs)**

The interaction of indacaterol, formoterol and salmeterol with the short acting adrenergic agent isoprenaline was evaluated by Naline et al. [16] on a nice study with isolated human bronchi. These authors show that indacaterol and formoterol behave as full agonists and do not antagonize the isoprenaline-induced bronchi relaxation response in an isolated human bronchi model using preparations precontracted with carbachol. The lack of antagonism with short-acting agonists may have potential clinical connotations regarding the use of SABA as rescue therapy in common clinical practice. Other findings from the study reported by Naline et al. [17] were that indacaterol showed an onset of action similar to that of salbutamol and duration of action > 12 hours.

**INDACATEROL**

Previous studies in patients and healthy volunteers have shown that LABAs may be associated with β\textsubscript{2} mediated systemic adverse effects such as skeletal muscle tremor, headache, nervousness, palpitations with changes in heart rate, prolongation of the QTc interval, and increased glucose and potassium blood levels [18-25]. On the basis of these data, safety and tolerability studies have been conducted to evaluate indacaterol effect on these parameters. An optimal safety profile is mandatory for a drug, such as indacaterol, characterized by a 24-hour bronchodilator efficacy at once-daily dosing.

In asthma patients’ indacaterol offers an excellent overall safety profile since even a high dose of 1000 μg has not been found to be associated with any sustained systemic adverse effect [26-28]. It is worthwhile pointing out that a dose of 1000 μg is obviously a clearly supratherapeutic dosing, which is five-fold the standard dose in asthma; this feature deserves to be emphasized since in clinical practice some patients may self-administer additional doses of the drug as rescue medication or accidentally.

In the COPD setting, once-daily indacaterol at doses up to 800 μg has been well tolerated. A prospective randomized comparative study on 163 patients with COPD receiving placebo or 400 μg or 800 μg of indacaterol did not show any statistically significant difference at any dose on mean pulse rate and QTc interval [29]. As it has been observed in safety studies in asthma population [30], small differences, considered to be without any clinical relevance, were found on serum potassium levels, mean blood glucose levels and mean blood pressure.

Although no serious adverse effects are found in safety studies on indacaterol, mild cough is a relatively common adverse effect [31]. A short duration, less than 2 minutes post-dose, and the lack of bronchospasm of any degree are distinctive features of this indacaterol-induced cough. It has been reported in up to 14.7% of patients receiving this inhaled drug at a dose of 400 μg daily and in up to 28.4% in those receiving an 800 μg daily dose. It is worthwhile remembering that an 800 μg dose represents at least 2 times the usual therapeutic dose suggested by initial studies. In a different series of COPD patients treated with more standard doses of indacaterol mild and short-lived cough occurred in a dose-related form, with an incidence that ranged from 2.9% with a 50 μg dose to 12.4% with a 400 μg dose. This cough is almost always of mild intensity; it usually appears with initial administration of the drug and declines progressively after a few days of treatment. In the study published by Rennard et al. [14] the incidence of cough by day 7 was similar to that observed with placebo. More interestingly, by the first month of treatment no patients receiving indacaterol complained about cough.

Researchers have realized that a very low drop-out rate has been consistently observed in the indacaterol arm of most comparative clinical trials, a data that suggests itself the
good safety and tolerability profile of this inhaled ultra-LABA. However, a word of caution is still warranted since a common pitfall of most new LABAs trials, including those that focus on indacaterol, is that the duration of the studies is in general relatively short. Consequently, more long-term studies are warranted to definitely confirm its impressive bronchodilator efficacy and continued safety over time.

PRESSURIZED METERED-DOSE INHALER (MDI) VERSUS SINGLE-DOSE DRY POWER INHALER (SDDPI)

Indacaterol has proven to be equally effective given either by hydrofluoroalkane (HFA) pressurized metered-dose inhaler or single-dose dry powder inhaler. A recent study on patients with COPD has established the SDDPI as the preferred system to inhale the drug and this device will be the usual way of administering indacaterol when the drug becomes commercially available [32]. Moreover, dosages used in this last study (150 µg, 300 µg and 600 µg) will also most likely be the recommended doses when the drug eventually comes out.

COMBINATION THERAPY WITH INDACATEROL AND NVA237 (GLYCOPYRROLATE)

As stated before, preliminary reports suggest that the combination of a LABA and a LAMA may provide a therapeutic benefit in some patients with chronic airflow obstructions although this potential benefit has not been consistently identified in all published studies that have addressed this issue. It well could be that the choice of both a determined long acting β2-adrenoceptor agonist and a long-acting muscarinic agent is one of the potentially crucial variables to explain some of the discrepancies found among different studies. A fixed dose combination of indacaterol and NVA237 for once-daily treatment of COPD is also under development. Ongoing clinical trials using this combination will certainly help to clarify this subject in the future.

There is some evidence suggesting an optimal safety profile for NVA237: a low systemic absorption is one of the pharmacokinetic characteristics of inhaled NVA237 and it is associated with a low effect of this drug on cardiovascular parameters when compared to tiotropium [33]. Although this finding supports a more favorable safety profile for NVA237 it still remains unclear if this difference really may imply any clinically significant impact on common clinical practice. Improvements in lung function with NVA237 seem to be comparable to those observed with tiotropium [34] but inhaled NVA237 does not produce the dry mouth side effect that is often reported with other antimuscarinic drugs. Phase III studies have shown a rapid onset, about 5 minutes post-dose, of bronchodilator effect. A sustained improvement if FEV1 has been observed when a dose ≥ 120 µg of NVA237 has been administered in these studies.

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