Role of arformoterol in the management of COPD

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Abstract: Formoterol is a beta2-agonist that has both short and long acting bronchodilator effects. Beta2-agonists used as bronchodilators have been synthesized as racemates that comprise (R,R) and (S,S)-enantiomers. Compounds that are beta2-selective derive their bronchodilator effect from an interaction between the (R,R)-enantiomer and the beta2-adrenoceptor. Arformoterol is the (R,R)-enantiomer and is distinguished from the more commonly used racemic (RR/S,S)-diasteriomer of formoterol. Overall literature on the use of arformoterol in COPD is very preliminary. There is some in vitro data that demonstrate significant bronchodilation and inhibition of inflammation with arformoterol, and these effects may be more pronounced than those caused by racemic formoterol. There are limited clinical trial data that demonstrate that arformoterol produces significant improvement in lung function in COPD; however, many of the subjects involved had marked baseline airway reversibility. Arformoterol has been very well tolerated in clinical trials and could potentially be used only once every 24 hours (due to its prolonged effect). It can only be given in nebulized form. Arformoterol can potentially be given with other inhaled medications.

Keywords: COPD, arformoterol, efficacy, safety

Introduction
Bronchodilators are first line treatment for chronic obstructive pulmonary disease (COPD) and have been shown to improve lung function, decrease exacerbation frequency and rescue medication use and patient symptoms, including dyspnea and health status (Mahler 2002; Appleton et al 2006). Bronchodilators may act as anticholinergic agents (eg, ipratropium bromide or tiotropium) or as beta2-agonists. The beta-agonists are divided into short-acting (SABA) and long-acting (LABA) forms. The LABA have two principal forms: salmeterol and formoterol.

Formoterol has been used for over 10 years, initially to treat asthmatic subjects. Recent publications have highlighted the potential use of formoterol, in combination with budesonide, as a single inhaled preparation for the treatment of asthma (O’Byrne et al 2005; Rabe et al 2006). Arformoterol is the (R,R) enantiomer of formoterol (Trofast et al 1991; Handley et al 2002). Preclinical studies have suggested that arformoterol is a more potent beta2-agonist than formoterol. Arformoterol is the only LABA available as an inhalational solution for use in a nebulizer (Baumgartner et al 2007).

This review will assess the different pharmacology/modes of action and clinical efficacy of arformoterol in comparison with other long-acting beta2-agonists.

Pharmacology
All beta2-agonists bind to beta2-adrenoceptors on bronchial smooth muscle. The amount of bronchodilator response is related to the concentration of the drug in the vicinity of the smooth muscle (except for salmeterol which is aliphatic) and the
degree of beta2-adrenoceptor activation. The long-acting beta2-agonists were first used in the 1980s (Johnson 1995). Salmeterol is a partial agonist at the beta2-adrenoceptor achieving maximum effect after 60 minutes (Brogden and Faulds 1991), whilst formoterol is a full agonist, achieving a more rapid onset of action with significant bronchodilator effect at 5 minutes, similar to short-acting beta2-agonists such as salbutamol (Bartow and Brogden 1998). Both drugs have durations of effect exceeding 12 hours and are recommended for regular use at 12 hourly intervals. Salmeterol and formoterol have differences in their chemical structures (Lotvall 2001). Formoterol has an additional methoxy group in the side chain which enhances signal transduction (Mak et al 1994; Roux et al 1996) when compared with salmeterol (accounting for the partial agonist effect). It has been suggested that the lipohicity of LABAs may allow access to the beta2-adrenoceptors for a prolonged period accounting for their duration of action (Anderson 1993).

Formoterol has been shown to have other effects on the airway apart from bronchodilatation. Formoterol inhibits plasma leakage in the airways through the beta2-receptor on the endothelial cells of post-capillary venules (Tokuyama et al 1991; Baluk and McDonald 1994) and sputum α-2 macroglobulin (Greiff et al 1998). Beta2-agonists including formoterol inhibit mediator release by mast cells, an important benefit in the treatment of asthma (Nightingale et al 1999; Ketchell et al 2002). Neutrophils have been demonstrated to be a key inflammatory cell in COPD (Barnes 2000). Beta2-adrenoceptors are expressed on human neutrophils and beta2-agonists inhibit the release of reactive oxygen species (Nielson 1987; Mirza et al 2002). Other studies have demonstrated that LABAs decrease bronchial neutrophils (Jeffery et al 2002; Maneechotesuwan et al 2005).

### Enantiomers of formoterol

Beta2-agonists used as bronchodilators have been formulated as racemates that comprise 50:50 mixtures of (R,R) and (S,S)-enantiomers (Handley et al 2002). Compounds that are beta2-selective derive their bronchodilator effect from an interaction between the (R,R)-enantiomer and the beta2-adrenoceptor (Waldeck 1993). Formoterol is a (R,R,S,S) diastereomer whilst arformoterol is a (R,R)-enantiomer. The (S,S)-enantiomer of formoterol may inhibit airway relaxation. The minimum lethal intravenous dose has been determined to be 100 mg/kg for (R,R)- and 50 mg/kg for (S,S)-formoterol suggesting that the toxicity of (S,S)-formoterol may not be related to the binding of the beta2-adrenoceptor (Handley et al 2002). These studies suggest that the arformoterol (R,R)-enantiomer) may be more efficacious bronchodilator than formoterol ([R,R/S,S] diastereomer). However, a study that assessed the (R,R), (S,S) and (R,S) found no difference in bronchodilator effect between (R,R)-formoterol and (R,S)-formoterol (Schmidt et al 2000). In contrast, another study found in sensitized guinea pigs that (R,R)-formoterol inhibited histamine and antigen-induced bronchoconstriction more than the racemate (Handley et al 2002).

Some studies have shown that beta2-agonists worsen asthma control by increasing airway inflammation (Cockcroft et al 1999). This effect may be influenced by different enantiomers, with the (R,R)-enantiomer being anti-inflammatory, and the (S,S)-enantiomer being proinflammatory. The (S,S)-enantiomer of albuterol mediates proinflammatory effects on T cells by interfering

<table>
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<tr>
<th>Effect on inflammatory mediators</th>
<th>(R,R)-isomer</th>
<th>(R,S)-isomer</th>
<th>(S,S)- isomer</th>
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<tbody>
<tr>
<td>IL-4</td>
<td>↓↑↑</td>
<td>–</td>
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<td>GM-CSF</td>
<td>↓↑↑</td>
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<td>IL-2</td>
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<td>IFN-γ</td>
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<td>IL-13</td>
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<td>IL-5</td>
<td>↓↑↑</td>
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<td>Fas ligand</td>
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**Note:** The (R,R)-isomer is arformoterol and the (R,S)-isomer is racemic formoterol.

**Abbreviations:** BD, bronchodilation; IL, interleukin; IFN-γ, interferon gamma; ↓, decreased; ↑, increased; –, no change.
with the anti-inflammatory effect of (R,R)-albuterol (Baramki et al 2002). The 2 different enantiomers of formoterol have also been shown to have different effects on inflammatory mediators; (R,R)-formoterol reduces levels of the inflammatory cytokine granulocyte macrophage-colony stimulating factor (GM-CSF) in human airway smooth muscle cells whilst (S,S)-formoterol increased levels of GM-CSF (Ameredes et al 2001) and levels of IL-4 in mast cells in a murine asthma model (Abraha et al 2004). Beta2-agonists interact with specific receptors on the surface of T lymphocytes (Ramer-Quinn et al 1997). Steinke et al assessed the effect of different formoterol enantiomers on T cell function in 10 healthy human controls (Steinke et al 2006). This study found that the (R,R) formoterol had predominantly anti-inflammatory effects on T cell function (proliferation and cytokine production) whilst the racemate had opposite effects. There appears to be no in vivo evidence about the different anti-inflammatory effects of racemates in the literature.

**Clinical efficacy**

**Formoterol for the treatment of COPD**

The introduction of the long acting beta2-agonists has been shown to be effective in COPD (Rabe et al 2007). Formoterol, with its unique properties of acute onset and prolonged bronchodilation effect, is potentially both a first-line reliever medication in addition to being maintenance therapy. The use of formoterol in COPD has been recently reviewed (Berger and Nadel 2008). Four randomized placebo-controlled trails of the use of formoterol in COPD have demonstrated improved lung function (FEV1, and peak expiratory flow rates) and symptoms (symptom score and exacerbations) and decreased need for rescue medication (Dahl et al 2001; Aalbers et al 2002; Rossi et al 2002; Campbell et al 2005). Anticholinergic agents may reduce severe exacerbations and mortality in COPD when compared with beta2-agonists (Salpeter et al 2006).

**Arformoterol for the treatment of COPD**

There have been two studies (published/in press) in journals assessing the effect of arformoterol in COPD (Baurgartner et al 2007; Hanrahan et al 2008). These were two identical, 12-week, double-blind randomized trials. Subjects were randomized to receive placebo, nebulized arformoterol (15 μg twice daily, 25 μg twice daily, 50 μg daily, and salmeterol metered dose inhaler (MDI) (42 μg twice daily). Subjects were followed up for 12 weeks and the percentage change in trough FEV1, percentage change in FEV1, average AUC (0–12 hours), and peak percentage change FEV1 from predose were analyzed. A total of more than 1400 subjects completed the trials, and similar results were obtained from both trials. The pooled data from these studies showed that the median time to achieve a 10% improvement in FEV1 from predose levels at week 12 was 3–13 minutes with nebulised arformoterol, and 142 minutes with salmeterol. Arformoterol 25 μg given twice daily was more effective than arformoterol 50 μg daily (percentage change in trough FEV1; 17.8% and 15.3%) but arformoterol 50 μg daily was similar to salmeterol 42 μg twice daily. After 12 weeks the 78%–87% of arformoterol subjects had a 10% increase in FEV1 compared with 56% salmeterol and 44% placebo. The results of these 2 large trials demonstrate that arformoterol is effective in improving lung function in COPD, perhaps more so than salmeterol. The major criticism of these trials is in the selection of the COPD subjects. The patients were selected

<table>
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<th>Findings</th>
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<tr>
<td>Baumgartner (2007)</td>
<td>1456</td>
<td>Randomized, placebo controlled, double-blind</td>
<td>Arformoterol, (30–50 μg) and salmeterol (84 μg) 12 weeks</td>
<td>Improvement in FEV1, 78%–87% of arformoterol and 44% of salmeterol group had &gt;10% improvement FEV1, improved symptoms and ↓ rescue medication for both</td>
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<td>Hanrahan (2007)</td>
<td>(2 combined trials)</td>
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<td>Hanrahan (2007)</td>
<td>39</td>
<td>Randomized, cross-over open-label</td>
<td>Arformoterol (15 μg), formoterol (12 and 24 μg)</td>
<td>Improvement in FEV1, similar with all doses</td>
</tr>
<tr>
<td>Baurgartner (2006)</td>
<td></td>
<td>Crossover, dose-ranging</td>
<td>Arformoterol (38–192 μg)</td>
<td>All dose ↑ FEV1, no benefit extra benefit above 48 μg</td>
</tr>
<tr>
<td>O’Donohue (2007)</td>
<td>813</td>
<td>Randomized, double-blind</td>
<td>Arformoterol (50 μg), salmeterol (84 μg) (12 months)</td>
<td>Improvement in FEV1, more with arformoterol and ↓ rescue medication for both</td>
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as having physician diagnosed nonasthmatic COPD. Subjects had all had a > than 15 pack-year smoking history with the average being >60 years and the mean FEV₁ of the group was 41% predicted. However, the mean airway reversibility of the group was 18.5% at randomization, suggesting that at least some subjects may have had coexistent asthma. Nonetheless, as lung volumes were low (baseline FEV₁ of 0.7 L), an 18.5% airway reversibility may not have been a definite criteria for asthma. There is no detail in this study as to how asthmatic subjects were excluded or whether the initial airway reversibility influenced trial outcomes. It would also have been of interest to have a racemic formoterol arm in the trial.

Several studies of the clinical efficacy of arformoterol have been presented at conferences and data are available in conference abstracts. An open label, randomized crossover study of arformoterol (15 μg) and racemic formoterol (12 μg and 24 μg) in 39 COPD subjects found similar improvements in lung function with all 3 doses (Hanrahan 2007). A crossover dose-ranging study in which COPD subjects received arformoterol at 9.6 μg 4 times daily, 24 μg twice daily, 48 μg 4 times daily or 96 μg twice daily compared with placebo found that all doses significantly improved FEV₁ and there was no added benefit to having a dose higher than 24 μg twice daily (Baumgartner et al 2006). An analysis of patient-centered outcomes in the two trials of 1456 COPD found patients experienced similar improvements in dyspnea, overall self reported functioning and decreased rescue medication for both arformoterol and salmeterol versus placebo (Hanrahan et al 2007). A 12 month trial was conducted to assess the effect of once daily arformoterol at a dose of 50 μg in 528 patients with COPD compared to a control group of 285 patients with COPD who were treated with salmeterol 42 μg twice daily (O’Donohue et al 2007). This study found that there was a decrease in rescue and supplemental medication with both forms of LABA and both improved trough FEV₁ over the 12-month period (arformoterol more so than salmeterol).

### Safety profile of arformoterol

The activation of the beta2-adrenoceptor may cause other effects in addition to bronchodilation including tachycardia, tremor, hypotension, hypokalaemia and hyperglycaemia (Rabe 2001). Despite these potential adverse reactions, beta2-agonists have been used successfully in most patients. The TORCH study found that salmeterol had no increase in mortality over a 3-year period compared with placebo (Calverley et al 2007).

As there are significantly fewer clinical data available on the use of arformoterol, the safety of this nebulized drug has not been as clearly established as that of racemic formoterol. In 2 clinical trials of 1400 patients over a 12-week period, arformoterol was well tolerated (Baumgartner et al 2006; Hanrahan et al 2008). For patients receiving arformoterol 15 μg bid and 25 μg bid, there was no increase in adverse events compared with placebo. In subjects receiving 50 μg daily of arformoterol there was a 3% increase in mild adverse events compared to control. There were no major adverse events reported. A study that assessed the use of racemic formoterol and arformoterol in asthma found both forms were well tolerated (Lotvall et al 2005).

Several other studies have been reported in abstract form. The effect of arformoterol on the QT interval of 215 patients with COPD was studied (Baumgartner et al 2007). A randomized double-blind trial was used to assess the effects of arformoterol given daily or twice daily (dose from 10 to 50 μg) and found there was no evidence of prolonging of cardiac depolarization. A 12 month trial was conducted to assess the effect of once daily arformoterol at a dose of

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<td>Arformoterol (30–50 μg) and salmeterol (84 μg) 12 weeks</td>
<td>Well tolerated, no changes compared to placebo in side effects, no cardiac issues, Mild tolerance</td>
</tr>
<tr>
<td>Hanrahan (2007)</td>
<td>Randomized, double-blind Placebo-controlled</td>
<td>Arformoterol (2–18 μg), racemic formoterol (4–36 μg)</td>
<td>Well tolerated, no difference in medications</td>
</tr>
<tr>
<td>Lotvall et al (2005)</td>
<td>Randomized, Double-blind</td>
<td>Arformoterol (10–50 μg)</td>
<td>No effect on cardiac depolarization</td>
</tr>
<tr>
<td>Baumgartner (2007)</td>
<td>Randomized, double-blind (12 months)</td>
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50 μg in 528 patients with COPD, compared with a control group of 285 patients with COPD who were treated with salmeterol 42 μg twice daily. The trial found both groups tolerated the medications well, and there was no change in heart rate (O’Donohue et al 2007).

Tolerance to long acting beta2-agonists has been described to nonspecific challenges (Cheung et al 1992), exercise (Simons et al 1997; Nelson et al 1998) and allergen (Giannini et al 1996). The clinical significance of tolerance is uncertain and seems to be confined to the early weeks of treatment (Lipworth et al 1998) and some bronchoprotection is maintained during long-term treatment (FitzGerald et al 1999). The bronchodilator response to racemic formoterol shows a small reduction during the initiation of treatment due to the rapid development of tolerance, but this does not progress (Yates et al 1995). A mild tolerance effect developed to arformoterol over a 12-week period (Hanrahan et al 2008).

Administration of arformoterol

Arformoterol can only be given by nebulizer, and is not approved by the Federal Drug Administration (FDA) for the treatment of acute exacerbations/rescue therapy. This does significantly restrict the use of this medication; probably mainly to patients who are unable or unwilling to use a dry powder inhalation (DPI) or metered dose inhaler (MDI) preparation of a LABA. Other potential groups who may use nebulized medication are 1) patients who have repeated episodes of airflow obstruction despite DPI/MDI use and 2) patients with severe lung function compromise (O’Donohue 1996).

New beta2-agonists are being developed: the ultra-long acting beta2-agonists, which can be given once a day, and this potential use has been reviewed recently (Matera et al 2007). A clinical study of arformoterol in asthmatic subjects described 24-hour duration of bronchodilator effect at higher doses (Vaikcus et al 2000). A subsequent study comparing arformoterol and racemic formoterol found with both drugs that bronchodilation was maintained beyond 12 hours with no significant differences between the two medications (Lotvall et al 2005). Several clinical studies of arformoterol have used a once daily dose of 50 μg with effective bronchodilation; this potential of the prolonged action of arformoterol was not discussed in these trials (O’Donohue et al 2007; Hanrahan et al 2008).

One potential use of arformoterol may be for the treatment of exacerbations of COPD. Its anti-inflammatory properties may be beneficial in addition to its bronchodilator effects for exacerbations. However, there are no clinical trial data about this, nor has its use been approved for this indication.

Many patients with COPD are treated with combined therapies. A recent study found that arformoterol was compatible with 3 other nebulized drugs: ipratropium bromide, acetylcysteine and budesonide (Bonasia et al 2007). This study did not assess the bronchodilator effects. Combining arformoterol with other inhaled medication may have benefits for some patients. The combination of long acting agents to produce a once daily inhaled medication may have significant benefits (Matera and Cazzola 2007).

Conclusion

Arformoterol is a newly developed long acting beta2-agonist given by nebulizer that has been approved for the maintenance treatment of COPD in the US. Arformoterol is the (R,R)-enantiomer of formoterol. There is a relative lack of published data about this medication. Being a (R,R)-enantiomer it may have more potent bronchodilator and anti-inflammatory properties than racemic (R,R/S,S)-formoterol. The clinical trials on the use of arformoterol, while limited in number, have generally been randomized and double-blinded with large numbers of subjects. The results have shown that arformoterol is a safe and effective bronchodilator in COPD, but these results should be interpreted in the light of a high incidence of significant baseline airway reversibility in trial subjects. There does not appear to be any major clinical differences between arformoterol and racemic-formoterol. The use of arformoterol is restricted by the requirement for nebulization. With its anti-inflammatory properties, arformoterol may have a role in the treatment of exacerbations of COPD.

Acknowledgments

The author would like to thank Dr JP Hanrahan (Serpracor, Massachusetts, USA) for supplying several references (Hanrahan 2007b, Hanrahan 2008, O’Donohue 2007).

Conflict of interest

The author declares no conflict of interest.

References


