

# Clinical potential of acclidinium bromide in chronic obstructive pulmonary disease

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**Abstract:** Chronic obstructive pulmonary disease (COPD) is increasing worldwide and is predicted to become the third most frequent cause of death by 2030. Muscarinic receptor antagonists, alone or in combination with long-acting  $\beta_2$ -agonists, are frequently used for COPD therapy. Acclidinium bromide is a novel muscarinic receptor antagonist, and clinical studies indicate that its metabolism is more rapid than that of other muscarinic receptor inhibitors, so systemic side effects are expected to occur less frequently. Acclidinium bromide is well tolerated, and when compared with other muscarinic receptor antagonists, the drug achieves better control of lung function, especially night-time symptoms in COPD patients. This review summarizes the safety profile and side effects reported by recent clinical studies using acclidinium bromide alone.

**Keywords:** acclidinium, tiotropium, side effects, clinical safety

## Introduction

It is estimated that nearly 3 million people worldwide die of chronic obstructive pulmonary disease (COPD) every year and the prevalence is increasing.<sup>1</sup> A major pathology of COPD is persistent irreversible constriction of the airways caused by smooth muscle cell activation. Bronchoconstriction in COPD reduces the airway lumen, thus limiting airflow.<sup>2</sup> Therefore, smooth muscle cell relaxation is the major target to ease breathing in COPD patients. In the past, bronchodilation has been achieved mainly by inhalation of a long acting  $\beta_2$ -agonist, but recent studies have provided evidence that blocking muscarinic receptors is more effective. However, use of the muscarinic receptor antagonists as therapeutics in COPD is not novel, but the previously available drugs had unwanted side effects, especially on the cardiovascular system.<sup>3,4</sup> Thus, novel long-acting muscarinic receptor antagonists have been developed in recent years, and have been proven to effectively reduce symptoms in COPD patients with less severe side effects in the cardiovascular system.<sup>5,6</sup> Here we provide a summary of the most recent clinical safety studies on the action of acclidinium bromide.

Bronchoconstriction is mainly due to constriction of smooth muscle cells in the airway wall, which can be triggered by activation of M3 receptors.<sup>7,8</sup> Therefore, blockade of M3 receptors is assumed to relax the muscle cells and ease breathing. Acclidinium bromide is a novel long-acting muscarinic receptor antagonist, which has been approved for COPD therapy. Preclinical studies showed the preference of acclidinium bromide for the M3 receptor over M2, M1, and M4 receptors.<sup>9</sup> Compared with other long-acting muscarinic receptor antagonists, acclidinium bromide has the advantage of being degraded rapidly and cleared from the circulation within 3 hours. Acclidinium bromide is hydrolyzed by butyrylcholinesterase into either carboxylic acid

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or alcohol metabolites, and thus results in fewer systemic side effects than other muscarinic receptor inhibitors, including tiotropium.<sup>9,10</sup> Based on preclinical and Phase I studies, it was concluded that acclidinium bromide would have fewer side effects than other muscarinic receptor antagonists, especially in the cardiovascular system.<sup>9–14</sup>

This review summarizes the safety profile of acclidinium bromide therapy in COPD patients as reported in recent clinical studies. The selection criterion was reporting of adverse effects in clinical studies, and case reports were not included. However, the available data on the side effects for acclidinium bromide are very limited.

## Clinical benefits of rapid acclidinium bromide metabolism

In a comparative study performed in different species, it was demonstrated that the metabolism of acclidinium bromide is most rapid in humans and dogs compared with guinea pigs and rats, while that of tiotropium was similar in all species.<sup>15,16</sup> A further study provided evidence that acclidinium bromide was degraded more rapidly than other muscarinic receptor antagonists, supporting the idea that the drug may have a lower incidence of side effects.<sup>17</sup> However, neither of these two studies explained on which enzymatic system this rapid turnover is based. When healthy volunteers inhaled 6,000 µg of acclidinium bromide, the compound was rapidly metabolized and not detectable in the circulation 3 hours later.<sup>12</sup> In a Phase I trial, 272 healthy volunteers inhaled 800 µg acclidinium bromide daily over a period of 3 days. The drug proved to be very safe with regard to the cardiovascular system and had no significant effect on electrocardiogram readings monitored over 24 hours. Similar to the earlier studies, the plasma concentration of acclidinium bromide was below the detection limit 2 hours after inhalation of the drug.<sup>18</sup>

In 16 healthy volunteers, the maximum tolerated dose of acclidinium bromide was determined by dry powder inhalation at ascending doses ranging from 600 µg to 6,000 µg, with dose increments separated by a washout period of 7 days.<sup>12</sup> The incidence of side effects was identical for acclidinium bromide and placebo, and included mild to moderate cardiac effects, which interestingly were not dose-related. The major side effects of acclidinium bromide were headache, fatigue, and renal pain, while airway obstruction, dry mouth, laryngitis, epistaxis, and acne were reported in two cases each. Like earlier studies, acclidinium bromide was rapidly metabolized and not detectable 3 hours after inhalation. The authors concluded

that acclidinium bromide is safe and well tolerated up to a single dose of 6,000 µg.<sup>12</sup>

In 2012, de la Motte et al<sup>11</sup> compared the pharmacokinetics and safety of acclidinium bromide in young and elderly COPD patients. The study included 12 patients aged 40–59 years and 12 patients older than 70 years. All patients inhaled acclidinium bromide 200 µg once daily over 3 days, followed by a second series of inhalations of acclidinium bromide 400 µg over 3 days after a washout period of 7 days. The results of this study showed that acclidinium bromide is rapidly degraded with no difference comparing young with elderly patients, and thereby confirmed the rapid degradation of acclidinium bromide, which had been reported by others.<sup>9,13,14,19</sup> The plasma concentration of acclidinium bromide was not detectable at time points later than 3 hours after inhalation and this effect was independent of age. Thus, the dose of acclidinium bromide does not have to be adjusted for age.<sup>11</sup>

## Side effects of acclidinium bromide

In a one-year study, 291 COPD patients inhaled acclidinium bromide 200 µg or 400 µg twice daily, which had very few side effects. In this cohort, less than 5% of patients reported cardiac side effects, and dry mouth was reported by only one patient.<sup>19</sup> All reported side effects were independent of dose and duration of treatment. Furthermore, using questionnaires, the patients indicated improved overall quality of life during the 52-week study, which was again independent of acclidinium bromide dose strength. Importantly, acclidinium bromide therapy significantly improved lung function. However, the authors admitted that their study may have been slightly biased by the fact that they selected their long-term study patients from a previous cohort of 467 COPD patients who had been treated with acclidinium bromide over a period of 12 weeks. The authors acknowledged that such selection of their patient cohort, which they assigned as “healthy survivors”, may have improved the safety outcomes for acclidinium bromide. Nevertheless, other studies have also confirmed the good safety profile of acclidinium bromide in long-term treatment.

A similar 52-week, double-blind study including 605 patients with moderate to severe COPD was reported by Gelb et al.<sup>20</sup> In this study, patients were randomized to inhalation of acclidinium bromide 200 µg or 400 µg twice daily. The reported side effects included dry mouth in 1.3% and 2.7% of patients and constipation in 2.9% and 1.7% at the respective dosages. Cardiac side effects were reported by less than 2% of patients, and as in the other studies, side effects were not related to drug dosage.

## Improved lung function with acclidinium bromide in COPD patients

Following on from the previous section, Gelb et al reported improved breathing capacity over a one-year study period in COPD patients, and the improvement in lung function correlated with the dosage of acclidinium bromide.<sup>20</sup> Furthermore, all COPD patients reported improved overall quality of life and better general health status.<sup>20</sup> Improvement in lung function as a result of long-term therapy with acclidinium bromide has also been reported by others.<sup>21–23</sup>

Comparing the clinical benefits of acclidinium bromide 400 µg, (morning and evening) with those of tiotropium (18 µg, morning) in 27 COPD patients, Fuhr et al<sup>24</sup> reported a similar bronchodilatory effect for both drugs. Furthermore, a significant reduction in night-time symptoms was achieved with acclidinium bromide but not with tiotropium. In a multicenter

study, the effects of twice-daily inhalation of 400 µg acclidinium bromide (morning, evening) were compared with once-daily inhalation of 18 µg tiotropium (morning) or placebo over a period of 6 weeks.<sup>25</sup> The authors determined FEV<sub>1</sub> AUC<sub>0–24</sub> and FEV<sub>1</sub> AUC<sub>12–24</sub> exacerbation in the different clinical centers and other COPD symptoms by questionnaire. The study comprised 440 patients recruited from 41 different sites, including the Czech Republic, Germany, Hungary, and Poland, who were randomized to treatment. Both drugs significantly increased the forced expiratory volume in one second compared with placebo. Acclidinium bromide showed a greater improvement in lung capacity than tiotropium after 6 weeks; however, the difference between the two drugs was not significant. The reduction of other COPD symptoms was clearly in favor of acclidinium bromide over tiotropium. Furthermore, only acclidinium bromide significantly reduced shortness of breath, wheeze, cough, phlegm, and night-time COPD symptoms.

**Table I** Recent clinical studies on the safety profile of acclidinium bromide

Subjects	n (age, years)	Dosage (µg) and duration	Side effects (n, relationship to dose if available)	Reference
Healthy	16 (range 18–65)	600, 1,200, 1,800, 2,400, 3,000, 3,600, 4,200, 4,800, 5,400, 6,000 Single dose 3 days 7-day washout	Headache (9) Fatigue (5) Renal pain (3) Dry mouth (1) Airway obstruction (1) Laryngitis (2) Epistaxis (2) Acne (2) None	Jansat et al <sup>12</sup>
Healthy	272 (range 18–45)	200, 800 Placebo Single dose 3 days	None	Lasseter et al <sup>18</sup>
COPD FEV <sub>1</sub> >30% and <80% FEV <sub>1</sub> /FVC <70%	12 (range 40–59) 12 (>70)	200, 400 Placebo Single dose 3 days 7-day washout	Headache (4/3) Fatigue (5/5) Dyspnea (2/1)	de la Motte et al <sup>11</sup>
COPD FEV <sub>1</sub> >30% and <80% FEV <sub>1</sub> /FVC <70%	27 (mean age 58)	Acclidinium 400 twice daily Tiotropium 18 once daily Placebo 15 days 9–15 days washout	Diarrhea, flatulence, pruritus, cough, pneumonia, syncope, contusion, fatigue, extremity pain	Fuhr et al <sup>24</sup>
COPD FEV <sub>1</sub> >30% and <80% FEV <sub>1</sub> /FVC <70%	602 (>40)	200, 400 Twice daily 52 weeks	Headache (11/11) Dry mouth (4/8) Dyspnea (8/2) Cardiac (24/12)	Gelb et al <sup>20</sup>
COPD	291 (mean age 63.6)	200, 400 Placebo Twice daily 52 weeks	Headache (3/3) Dyspnea (5/2) Cardiac (0/1)	D'Urzo et al <sup>19</sup>
COPD FEV <sub>1</sub> >30% and <80% FEV <sub>1</sub> /FVC <70%	414 (mean age 62)	Acclidinium 440 twice daily Tiotropium 18 once daily Placebo 6 weeks	Not described	Beier et al <sup>25</sup>

**Abbreviations:** COPD, chronic obstructive pulmonary disease; FEV<sub>1</sub>, forced expiratory volume in one second; FVC, forced vital capacity.

Adverse effects were similar for all treatments, and thus could not be related to the drugs. Drug-related side effects were below 3% and similar for both drugs.<sup>25</sup> Finally, the US Food and Drug Administration concluded that the mortality rate under acclidinium bromide treatment does not differ between doses and was the same as with placebo control.<sup>26</sup>

## Conclusion and future perspectives

All published clinical trials indicate that acclidinium bromide is well tolerated and safe for use as long-term COPD therapy. An overview of the studies on acclidinium bromide is provided in Table 1. However, the mechanism(s) by which acclidinium bromide achieves its clinical benefits has to be studied further.<sup>27</sup> Studies in animal models and in human cells indicate that the beneficial clinical effect of acclidinium bromide in COPD therapy might involve more than antagonism of muscarinic receptors and muscle relaxation. These studies indicate that acclidinium bromide modifies cell differentiation, which manifests as epithelial–mesenchymal transition, a mechanism that contributes significantly to the pathogenesis of COPD.<sup>28–30</sup> Furthermore, when combined with a long-acting  $\beta_2$ -agonist, the beneficial effects of acclidinium bromide are increased further. In this regard, it will be interesting to see whether the combination of acclidinium bromide with a long-acting  $\beta_2$  agonist will further improve its benefits in COPD therapy.<sup>22,31,32</sup>

## Disclosure

The authors report no conflicts of interest in this work.

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