Clinical Pharmacology of Oral Maintenance Therapies for Obstructive Lung Diseases

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Although inhaled therapies are typically preferred for the maintenance treatment of obstructive lung diseases, oral drug therapies can also play valuable roles. The most commonly used oral agents are phosphodiesterase inhibitors, theophylline, macrolides, leukotriene modifiers, and mucoactive agents. Advantages of these oral agents include the unique pharmacologic mechanisms of action, the avoidance of the challenges of proper inhalational lung administration, and, in most instances, relative drug cost. For many of these agents, anti-inflammatory or immunomodulatory effects are the predominant pharmacologic mechanism that each provides clinical benefit, with the exception

of guaifenesin. In addition, theophylline, leukotriene modifiers, chronic macrolides, phosphodiesterase inhibitors, and N-acetylcysteine have been shown to decrease exacerbations in obstructive lung disease. Fairly rapid bronchodilation occurs with the phosphodiesterase inhibitors, theophylline, and leukotriene modifiers, although less than that achieved with inhaled therapies. The clinical roles of phosphodiesterase inhibitors, specifically roflumilast, and macrolides continues to be defined today, whereas the roles theophylline and leukotriene modifiers have probably been largely delineated. Azithromycin is the principal macrolide used chronically for obstructive lung diseases, especially COPD. Although guaifenesin is used widely, its effectiveness is unclear, whereas N-acetylcysteine currently has strong evidence supporting a decreased risk of COPD exacerbations. Mucolytic agents like N-acetylcysteine are used more widely outside the United States in obstructive lung diseases. *Key words: COPD; asthma; macrolides; leukotriene antagonists; expectorants; mucolytics; theophylline; roflumilast; phosphodiesterase inhibitors.* [Respir Care 2018;63(6):671–689. © 2018 Daedalus Enterprises]

Introduction

Because of the efficacy associated with direct delivery of medications into the lower respiratory tract, potentially faster onset of action, and the greater risk for systemic adverse effects with oral agents, inhaled drugs have evolved into first-line maintenance therapies for the treatment of obstructive lung diseases, whereas oral agents are typically used as second- or third-line agents. The oral maintenance agents most commonly used in the treatment of COPD and asthma include phosphodiesterase (PDE) inhibitors, theophylline, chronic macrolides, leukotriene modifiers, and mucoactive agents. Oral agents do have some advantages, including delivery to parts of the lungs that inhaled agents may not reach, different mechanisms of action, ease of administration compared to the inhaled route, and, for most of the agents, lower cost (Table 1). This review provides an overview of the clinical pharmacology of these agents, including mechanism of action, pharmacokinetics, pharmacodynamics, drug interactions, dosing, and adverse reactions. Oral β_2 agonists are not covered due to their infrequent use in the United States.

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Phosphodiesterase Inhibitors

Although PDE inhibitors have been in development for many years, roflumilast (Daliresp, AstraZeneca, Cambridge, UK) has only been available in the United States since 2011 (Table 2). Roflumilast has been studied in asthma,[1] but it has not been cleared by the U.S. Food and Drug Administration (FDA) for this indication. Consistent with the product labeling, the 2017 Global Initiative for Obstructive Lung Disease (GOLD) 2018 COPD guidelines recommend roflumilast as an option to add to inhaled maintenance therapies, such as inhaled corticosteroids (ICS) and long-acting bronchodilators, in severe or very severe cases of COPD with chronic bronchitis symptoms and frequent exacerbations (the historic blue bloater phenotype).[2] These patients are most commonly in GOLD Group D and tend to be smokers. Meta-analyses on preventing COPD exacerbations shows that roflumilast reduces the frequency and proportion of patients with COPD exacerbations over a 1-y period.[3,4] An upcoming Patient-Centered Outcomes Research Institute study will compare the effectiveness of azithromycin to roflumilast on COPD exacerbations.[5] It is unclear how theophylline, a broad-spectrum (non-selective) PDE inhibitor, compares clinically to roflumilast because a comparative study has not been published. Other PDE inhibitors are in development.

Mechanism of Action

Roflumilast is a narrow-spectrum phosphodiesterase-4 (PDE4) inhibitor that principally functions as an anti-inflammatory agent with minimal bronchodilator effects.[6,7] The major metabolite of roflumilast (roflumilast N-oxide) accounts for most of the pharmacologic effects of this agent.[7] As a selective PDE4 inhibitor, roflumilast works by increasing the second messenger molecule intracellular 3′5′-cyclic adenosine monophosphate (cAMP).

Table 1. Approximate Retail Costs of Oral Maintenance Therapies and Representative Proprietary Inhalers in the United States

Drug/Device	Cost
Advair Diskus 250/Symbicort 160 pMDI, 1-month supply	$375
Roflumilast (Daliresp) 500 μg, 30 tablets	$350
Montelukast 10 mg, 30 tablets	$60
Zafirlukast 20 mg, 60 tablets	$50
Zileuton CR 600 mg, 60–120 tablets	$1,875–3,500
Azithromycin 500 mg, 20 tablets	$50
Theophylline ER 300 mg, 30 tablets	$40
N-Acetylcysteine 600 mg, 100 capsules	$6
Guiafenesin 600 mg (Mucinex) ER, 120 tablets	$70

Cost information from GoodRX, https://www.goodrx.com, *Accessed May 2017.* Currency is U.S. dollars.
pMDI = pressurized metered-dose inhaler
ER = extended release

Table 2. Key Points About Roflumilast

Indication	COPD, not cleared for asthma
Mechanism	Phosphodiesterase-4 inhibition leading to anti-inflammatory effects and mild bronchodilation
Clinical role	Decrease COPD exacerbations in advanced chronic bronchitis phenotype; improve quality of life; additive effects with inhaled maintenance therapies
Dosing	500 μg daily, given with food or 250 μg daily × 4 weeks, then 500 μg daily
Key drug interactions	3A4 and 1A2 inhibitors and inducers such as erythromycin
Main adverse effects (dose-dependent)	Gastrointestinal, weight loss, headache

cAMP is rapidly metabolized by PDEs, therefore inhibitors of PDEs, such as roflumilast, increase levels of cAMP. Increased levels of cellular cAMP enhance airway smooth muscle relaxation and can suppress inflammation. Roflumilast has been shown to decrease the release of inflammatory cytokines and mediators from various inflammatory cells including eosinophils, mast cells, neutrophils, and macrophages.[7] In COPD subjects roflumilast 500 μg oral daily over 1 month decreased sputum neutrophils and eosinophils by 31% and 42%, respectively.[8] In asthma, roflumilast can inhibit the late asthmatic response.[9]

The main clinical benefit of roflumilast in COPD is the reduction of exacerbations, although symptom improvement and a modest increase in FEV_1 can also be achieved.[6] Roflumilast is additive to the clinical effects of ICS/long-acting β agonists (LABA) and ICS/LABA/long-acting muscarinic agents (LAMA) regimens in COPD.[10]

Pharmacokinetics and Pharmacodynamics

The oral bioavailability of roflumilast is ~80%, and although food delays absorption, it does not decrease the extent of absorption.[11,12] Therefore, taking roflumilast with food may improve gastrointestinal (GI) tolerability. Roflumilast is eliminated through hepatic metabolism by CYP1A2 and CYP3A4, primarily to the active metabolite roflumilast N-oxide. After an oral dose, the half-life of roflumilast and its N-oxide metabolite are approximately 17 h and 30 h, respectively, which means that steady-state plasma concentrations are reached in < 1 week.[13] Roflumilast is highly bound to plasma proteins (99%) and has a large volume of distribution, suggesting significant tissue penetration. With regard to liver disease, roflumilast was studied in subjects with mild-to-moderate hepatic impairment (Child-Pugh A and B) where the area under the serum concentration time curves for roflumilast and roflumilast N-oxide were increased by 51–92% and 24–41%, respectively.[14] Renal clearance is minimal for roflumilast, thus dosing adjustments are not necessary, although use in end-stage renal disease may warrant closer monitoring for adverse effects.

Regarding pharmacodynamics, some effects of roflumilast appear to be dose-dependent, including cellular and clinical effects, efficacy, and adverse effects. In an in vitro study using resected lung tissue, roflumliast and roflumilast N-oxide inhibited release of chemokines and TNF-α from lung macrophages in a dose-dependent manner.[15] Dose-dependent changes of this agent have also been observed regarding the release of matrix metalloproteinase-9 and neutrophil elastase, 2 important substances associated with inflammation in COPD.[7] One placebo-controlled study compared 2 different doses of roflumilast (250 μg and 500 μg once daily) in > 1,400 subjects with mild-to-moderate COPD; there was a statistically significant, dose-dependent improvement in FEV_1 and exacerbations.[16] Adverse effects appear to be more common with the 500 μg daily dose than with the 250 μg daily dose[16]; such effects also tend to be worse during the first 1–2 weeks after initiating therapy, and then they usually lessen.

Drug Interactions

Roflumilast is a substrate for agents that impair or induce metabolism by CYP3A4 or CYP1A2.[14] In contrast, therapeutic plasma concentrations of roflumilast or roflumliast N-oxide do not inhibit metabolizing enzymes such as CYP1A2, 2C9, 2C19, 2D6, or the P-glycoprotein transporter. Among the different drug-interaction studies conducted, 2-week courses of erythromycin and ketoconazole, both CYP3A4 inhibitors, were shown to increase roflumilast area under the serum concentration by 70% and 99%, respectively, in healthy volunteers.[17,18] It is recommended

Table 3. Key Points About Theophylline

Indication	COPD, asthma
Mechanism	Broad-spectrum phosphodiesterase inhibition, adenosine antagonist leading to anti-inflammatory effects, mild bronchodilation; aids diaphragm function; respiratory stimulant; increases mucociliary clearance and decreases cough
Clinical role	Add-on therapy primarily in advanced COPD, less frequently in asthma; may be additive with other COPD therapies; symptom relief, improved quality of life, and possible decrease in COPD exacerbations
Dosing	Low doses such as 100–200 mg twice daily as sustained release; target blood levels < 10 μg/mL; best to titrate dose upward upon initiation; monitor blood levels as indicated for suspicion of toxicity
Key drug interactions	Numerous through CYP1A2 and CYP3A4 inhibitors and inducers, such as ciprofloxacin
Main adverse effects (dose-dependent)	Gastrointestinal (nausea, vomiting, discomfort), central nervous system (headache, sleeplessness, seizures)

that the following drugs be given cautiously in persons receiving roflumilast: cimetidine, erythromycin, ketoconazole, fluvoaxamine, enoxacin, and Minulet (gestodene and ethinylestradiol; Pfizer, New York).[14] There are no data evaluating the potential interaction between roflumilast and grapefruit juice (flavonoids), although this could be clinically relevant for roflumliast through CYP3A4 inihibition. It is also recommended that the strong enzyme inducer rifampin is not given with roflumilast.[19] Drug interaction studies in healthy volunteers with roflumilast indicate dosage adjustments are not recommended when given concomitantly with warfarin, theophylline, or digoxin,[14] although such studies do not always predict interactions in patients, particularly the elderly. Although not recommended by the manufacturer, because of the 99% binding of roflumilast to albumin it is reasonable to monitor warfarin effects more closely for a short time period after starting roflumilast.

Dosing

The current recommended dose of oral roflumilast for treatment of COPD is 500 μg once daily, given with or without food.[14] A recent study comparing the efficacy of starting with 250 μg daily for 1 month and then increasing to 500 μg daily versus starting with 500 μg daily showed the higher dose to be more efficacious, although less well-tolerated.[20] This study led to the clearance of this dosing strategy of roflumilast in the United States. Daliresp is available in 250 μg and 500 μg strengths now. In the US, Daliresp, is not film-coated,[14] and the 500 μg tablet can be split. So patients can receive the 250 μg strength. The European version, Daxas, is a film-coated tablet thus should not be split.[21] This strategy has not been studied, although it is common to split tablets to allow lower doses of various non-sustained release or non-specially coated products, despite the lack of published evidence in most instances.

Adverse Effects

GI and central nervous system symptoms appear to be the most common adverse effects for roflumilast.[6] GI effects include diarrhea, nausea, and abdominal pain, whereas neurological effects include headache, sleeplessness, and nausea. The recent study comparing the 3 different dosing strategies found the regimen of 250 μg daily for one month, then 500 μg daily to be the best tolerated regimen when initiating therapy.[21]

In clinical trials, roflumilast has been associated with weight loss in $\sim$10% of subjects.[14] Potential mechanisms include nausea and anorexia as well as an increase in energy expenditure.[22] Therefore, in COPD patients with lower body mass index, such as many advanced emphysematous patients, should either not receive roflumilast or have weight and adverse GI effects monitored closely. Suicide was rarely reported in clinical trials in both the roflumilast and placebo group; however, the causality of suicide risk is unclear at present.[14]

Theophylline

Theophylline (3-methyxanthine) was one of the first synthesized oral agents used for the treatment of asthma, initially as aminophylline in the 1940s. It became popular in the 1970s and 1980s with the availability of sustained-release products and commercial automated assays that allowed convenient blood-level monitoring. When used for bronchodilator effects, the relatively high doses used at that time were associated with usually minor but sometimes severe GI, cardiac, and central nervous system adverse effects (Table 3). If blood concentrations became too high due to dosing or drug interactions, then seizures, cardiac arrhythmias, and even death could occur. Ultimately, the use of theophylline declined as inhaled LABAs became available. Today, theophylline is usually dosed at lower concentrations based on its anti-inflammatory effects in COPD achieved and thus is a safer option than in the past. It is used less often in asthma patients, but it is given in similarly low doses. The pharmacology of theophylline has been extensively studied in many patients, disease types, and settings.

The Global Initiative for Asthma (GINA) guidelines recommend that theophylline be considered an alternative

to ICS in uncontrolled asthma in adolescents and adults.[23] GINA also states that theophylline has weak efficacy in asthma and can be associated with severe adverse effects, and it therefore should not be used routinely for the treatment of chronic asthma. GINA recommends against the use theophylline in acute asthma, and further sustained-release theophylline is recommended for use when asthma control cannot be achieved with other bronchodilators. The National Asthma Education and Prevention program guidelines recommend sustained-release theophylline as an alternative, not as a preferred, therapy for step 2 care (for mild persistent asthma) or as adjunctive therapy with ICS in patients > 12 y old.[24] In some parts of the world, theophylline is used more frequently than in the United States. The Japanese asthma guidelines recommend intravenous theophylline as an option in acute asthma, and theophylline is included in the recommended options for persistent asthma.[25]

The GOLD guidelines do not recommend intravenous aminophylline in patients hospitalized with COPD due to significant adverse effects.[2] GOLD states that theophylline exerts small bronchodilatory effects in COPD and can provide modest symptom improvement. GOLD does not recommend the use of theophylline as a long-term controller for COPD unless other agents are not available or are unaffordable. Notably, in underserved countries, oral theophylline can be much cheaper than even inhaled albuterol.

Mechanism of Action

Theophylline has a number of pharmacologic effects including directly relaxing human airway smooth muscle, resulting in relatively weak bronchodilator effects (increased FEV_1), a respiratory stimulant effect, diaphragmatic contractility improvement, and anti-inflammatory properties.[26] One molecular mechanism of bronchodilation is weak, non-selective inhibition of PDE3 and PDE4. In addition, theophylline is a potent non-selective inhibitor of adenosine receptors (primarily A1 and A2) at therapeutic concentrations, which exert some anti-inflammatory effects.[26]

The anti-inflammatory and immunomodulatory effects of theophylline are multiple.[27,28] It has an inhibitory effect on superoxide anion release from human neutrophils and inhibits the feedback stimulatory effect of adenosine on neutrophils in vivo. In patients with COPD, theophylline reduces the total number and proportion of neutrophils in induced sputum, the concentration of interleukin-8, and neutrophil chemotactic responses.[29] Theophylline has several actions on T lymphocyte function, suggesting that it might have an immunomodulatory effect in asthma. In patients with mild asthma, low theophylline blood levels reduce the numbers of eosinophils in bronchial biopsies, bronchoalveolar lavage, and induced sputum.[30] In allergen challenge studies, theophylline inhibits the early and late asthmatic response.[31] Whereas the bronchodilatory effect of theophylline occurs within hours, the anti-inflammatory effects are more delayed. Anti-inflammatory effects are in part due to histone deacetylase activation, resulting in switching off of activated inflammatory genes. Research suggests that steroid resistance in patients who are smokers can be lessened with theophylline through its effects on histone deacetylase.[32]

From a clinical perspective, theophylline can improve FEV_1, respiratory symptoms, and allow lower doses of ICS for patients with asthma.[26] For patients with COPD, theophylline can improve FEV_1, air trapping, decrease work of breathing by affecting the diaphragm, as well as lower P_{aCO_2} and increase P_{aO_2}. A 2005 meta-analysis of 20 placebo-controlled studies, which represents the majority of current published clinical efficacy studies, reported that theophylline statistically improved FEV_1 (~100 mL), FVC, P_{aO_2}, and P_{aCO_2}.[33] Theophylline has also been shown to help improve mucociliary clearance,[34] inhibit the cough reflex,[35] and improve diaphragmatic function in COPD.[36]

Pharmacokinetics and Pharmacodynamics

Theophylline, including oral sustained-release products, is rapidly and completely absorbed when administered orally under fasting conditions.[37] Aminophylline, which is 80% theophylline, is also well absorbed when administered orally. Theophylline is primarily eliminated by hepatic biotransformation, predominantly by CYP1A2 but also by CYP3A4 and via urinary excretion (10–15%).[38]

At higher doses, theophylline can exhibit non-linear pharmacokinetics, causing blood levels to increase disproportionately. Although blood concentrations are determined mainly by hepatic metabolism, they may also be increased in several diseases (eg, congestive heart failure, liver disease) and by concomitant drug therapy.[38] In adults the typical half-life is about 8 h, but in advanced heart failure or liver disease, the half-life can approach 24 h. Viral infections can be an important source of impaired theophylline metabolism, partially due to increased levels of interferon that occurs with viral infection. The volume of distribution of theophylline correlates better with lean or adjusted body weight than with total body weight; therefore, dosing should not be based on actual body weight in morbidly obese patients.

Theophylline has a narrow therapeutic index; serum levels significantly above target range may lead to serious toxicity.[27,38] Early studies of theophylline indicated that blood levels in the range of 10–20 μg/mL were optimal for efficacy; this was based primarily on the hospitalized asthma population.[39] The bronchodilator response of theophylline was considered to be directly proportional to the

logarithm of the serum concentration.[40] Later, data from patients with COPD showed that FEV_1, FVC, and peak expiratory flow change only slightly (approximately 13%) over the range of doses associated with steady-state serum theophylline concentrations of 5–10, 10–15, and 15–20 μg/mL.[41] However, in this study a steeper dose-response for changes in volume of air trapped was observed, with 50% of changes occurring between the low and high theophylline blood levels. This may explain why theophylline may be useful in some patients with advanced COPD. There also appears to be a dose-response for the effects on the diaphragm contractility where blood levels > 10 μg/mL are more efficacious.[36] However theophylline is dosed today primarily for its ant-inflammatory effects, and maintaining blood levels of theophylline as low as 5 μg/mL is efficacious in patients with asthma and COPD.[42] By targeting these lower blood levels, drug interactions or changes in a patient's drug clearance for other reasons are less likely to result in toxicity.

Drug Interactions

There are numerous drug interactions with theophylline, largely due to alterations in hepatic metabolism, primarily with the CYP1A2 but also the CYP3A4 metabolizing enzymes.[43] Interacting drugs that tend to be prescribed in the COPD and asthma patient populations include the inhibitors cimetidine, ciprofloxacin, erythromycin, and clarithromycin, as well as the inducer rifampin. Whenever theophylline is used, drug interactions should be considered. A pharmacodynamic drug interaction also exists with parenteral adenosine in the treatment of atrial fibrillation, whereby its effectiveness can be decreased by theophylline (via adenosine antagonism). Inhalation of hydrocarbons in significant doses, most commonly from cigarettes, can induce theophylline metabolism quite substantially.[44] Thus, if a patient is receiving theophylline and quits smoking, then blood levels should be expected to increase within a week.

Dosing

Theophylline is now principally used in the out-patient setting as a generic, oral, sustained-release formulation, typically given twice daily. Considering the low target blood levels in the 5–10 μg/mL range that are used today, doses of 200–400 mg per day (~3 mg/kg/d lean body weight) will suffice in most patients. When initiating theophylline, it is usually better tolerated if the dose is titrated upwards (eg, if the target dose is 200 mg per day, start with 100 mg per day of extended-release generic theophylline for 1–2 weeks, then increase to 100 mg twice daily). Theophylline is best avoided in patients with right- and/or left-sided heart failure or significant hepatic dysfunction, because in such cases theophylline clearance can be severely impaired and varies.

Since 2016, there has been a shortage of generic oral sustained-release theophylline products by most manufacturers. However, Alembic Pharmaceuticals (Bridgewater, New Jersey) continues the manufacture of extended-release theophylline tablets (300 mg and 450 mg).[37] Because most patients will likely only need 300 mg/d, splitting the tablet in half and dosing as 150 mg twice daily is a reasonable strategy. The extended release formulation manufactured by Alembic Pharmaceuticals is a matrix sustained-release formulation, allowing it to be split in half with a pill splitter without compromising the sustained-release characteristics.[45]

Adverse Effects

Concentration-dependent adverse effects of theophylline can occur at any point during therapy.[27] Caffeine-like adverse effects tend to occur early in therapy, even at low doses, and these include sleep disturbance, tremors, headache, and nausea. If a patient develops unexplained nausea or vomiting while on theophylline, especially after the initiation phase, assessment of blood levels and reducing the dose or possibly stopping the drug may be warranted. Nausea, vomiting, and headaches may be due to PDE inhibition, and at higher concentrations cardiac arrhythmias and seizures may be related to adenosine A1-receptor antagonism.[27] In addition theophylline can increase gastric acid secretion and reflux, thus causing or exacerbating gastroesophageal reflux disease.

Azithromycin

Chronic macrolides are used in COPD, pan-bronchiolitis, cystic fibrosis, and bronchiectasis principally for the immunomodulatory, anti-inflammatory, and mucolytic effects.[45] They have also been studied in a number of other conditions such as asthma, post-transplant bronchiolitis obliterans, and post-myocardial infarction (anti-artherogenesis effects).[45] Substantial benefit has also been shown in cystic fibrosis, where exacerbations are decreased, quality of life is improved, and FEV_1 is increased.[46] Among erythromycin, clarithromycin, and azithromycin, the latter currently has the bulk of scientific evidence and clinical experience supporting its role as a maintenance therapy in chronic lung diseases (Table 4). In the 1950s, it was first noted that asthma patients had improved symptoms when prescribed erythromycin or trolandeomycin. Shortly thereafter, studies showed that these agents, including clarithromycin, had steroid-sparing effects, in part due to decreased hepatic metabolism of systemic steroids.[47] Numerous in vitro studies have demonstrated that all 3 macrolides have anti-inflammatory and immunomodulatory effects.[45]

Table 4. Key Points About Azithromycin

Indication	COPD (not FDA-cleared) and asthma (less established)
Mechanism	Immunomodulatory, ant-inflammatory, anti-bacterial; high concentrations in inflammatory cells and tissues facilitate activity
Clinical role	Decrease COPD exacerbations; limited data indicate patients with mild COPD and non-smokers are more likely to show benefits; use in combination with inhaled maintenance medications
Dosing	250–500 mg, daily to 3 times/week
Key drug interactions	Low potential for azithromycin, may include warfarin
Main adverse effects (dose dependent)	Gastrointestinal, prolonged QTc (relatively minimal risk), hearing impairment (infrequent, often minor, usually reversible)

QTc = QT interval corrected for heart rate (time between Q wave and T wave in the heart's electrical cycle)

In the 1990s and in early 2000s, data started emerging supporting the use of azithromycin and other macrolides for COPD.

GOLD reports that azithromycin 250 mg daily or 500 mg 3 times/week can be effective in reducing exacerbations in COPD, although it is also associated with increased bacterial resistance and hearing test abnormalities.[2] The current GINA guideline does not make any recommendations regarding macrolides for asthma.[23] Studies of macrolides in asthma have shown variability in clinical benefits.[48-50] The relative positive effects of macrolides on neutrophils, dominant in COPD, and relatively fewer effects on eosinophils may partially explain this difference seen in asthma. However, a recently published Australian study showed benefits of azithromycin in eosinophilic as well as non-eosinophilic asthma by reducing exacerbations in a larger number of subjects (1.1 vs 1.9 exacerbations/y).[50] Chronic macrolides may someday hold a similar clinical role in asthma as in COPD; it may be a function of determining the specific responsive phenotypes or genotypes. The potential effects of antibiotics on decreasing the effectiveness of oral contraceptives may be a factor for the use of these agents in potential child-bearing women with asthma.

Mechanism of Action

Chronic macrolides are used in COPD primarily for their immunomodulatory and anti-inflammatory effects[47,51,52] Accumulating substantially in cells, macrolides like azithromycin and clarithromycin exert effects on numerous cells (particularly neutrophils and macrophages) and mediators where concentrations in these cells are much higher than extracellular fluids. Macrolides have also been shown to relax constricted airway smooth muscle.[53] Immunomodulatory effects that have been described include reduced accumulation of pro-inflammatory mediators and modulation of neutrophil function and apoptosis. Macrolides have also been shown to influence the release of cytokines such as interleukin-8 and tumor necrosis factor as well as to inhibit leukocyte chemotaxis by suppressing synthesis of endogenous chemotactic factors.

Some of the clinical benefits that may occur with azithromycin in COPD are a reduction in number of exacerbations, improved respiratory symptoms, and improved quality of life in some patients.[52] In my experience, most COPD patients cannot discern the improvement in symptoms (especially compared to inhaled drugs), so I counsel that the primary role of this drug is to decrease exacerbations to aid compliance. It has been reported that current smokers are less likely to show a reduction in exacerbations with azithromycin than are non-smokers and patients with milder COPD severity.[54] Additional effects of azithromycin include reduction in the biofilm layer of bacteria like *Pseudomonas*, which can colonize in some COPD patients, especially in the presence of bronchiectasis or on chronic prednisone. Steroid-sparing effects have been shown for erythromycin and clarithromycin, at least partially because both are strong inhibitors of CYP3A4 substrates (eg, oral and inhaled corticosteroids) and both exhibit immunomodulatory and anti-inflammatory effects.[45]

Today, chronic azithromycin is considered to be an effective option for decreasing COPD exacerbations.[55,56] GOLD states that a macrolide can be added to a patient's drug regimen if still experiencing exacerbations despite inhaled triple therapy (ICS, long-acting anti-muscarinic and LABA).[2] Based on drug costs, it may be the most cost-effective therapy for prevention of COPD exacerbations.

Pharmacokinetics and Pharmacodynamics

The pharmacokinetic properties of macrolide antibiotics differ based on their chemical structure. Azithromycin, a derivative of erythromycin, is a 15-member azalide that has a much longer half-life than erythromycin and clarithromycin.[51] Oral, rapid-release azithromycin has low oral bioavailability of ~18–37%, and administration with food does not appear to affect its absorption.[57] The very long half-life of > 70 h, allows for shorter courses of treatment for some acute infections and less frequent dosing for some chronic uses. The protein binding is modest (30%) and it is extensively distributed in tissues and phagocytic cells such as macrophages and neutrophils. The high concentrations of azithromycin in these cells increases delivery of drug to sites of infection and inflammation. Azithromycin metabolism is marginal, and is minimally

excreted through the kidneys – the vast majority of the drug is eliminated through the biliary tract and feces.[57]

Combined with their good tissue penetration, including significant uptake into neutrophils, macrolides have favorable pharmacodynamic properties as immunomodulatory and anti-inflammatory agents in COPD. There are no clinical studies directly comparing different doses of azithromycin in COPD therefore there are no dose-response data to determine the most efficacious and safest dosage regimen for maintenance therapy. Most clinical studies have used either 250 mg daily or 500 mg 3 times/week.[58] One study in COPD found that azithromycin 250 mg 3 times/week decreased cough.[59] There is some in vitro evidence of dose-response effects of azithromycin on inflammation.[47,53] The GI and perhaps the rare cardiac adverse effects of azithromycin do appear to be dose-related.

Drug Interactions

Macrolides differ in their abilities to bind to and inhibit CYP3A4. In contrast to erythromycin and clarithromycin, azithromycin has been shown to interfere poorly with the cytochrome P-450 system in vitro.[60,61] Numerous drug interaction studies have been performed that essentially show a very low risk of altered drug clearance associated with the administration of azithromycin.[60,61] Based on spontaneous reports, there is a potential interaction between azithromycin and warfarin, but this appears to be less likely than with clarithromycin or erythromycin.

Dosing

Among published clinical studies, the doses of chronic azithromycin used for COPD range from 250–500 mg 3 times/week to 250–500 mg daily, the latter essentially representing treatment doses. The COLUMBUS study, which showed a decrease in exacerbations compared to placebo, used 500 mg daily,[56] but tolerability of this dose can be problematic. The European Respiratory Society/American Thoracic Society COPD exacerbation prevention guidelines recommend 250 mg daily or 500 mg 3 times/week.[58] Despite limited direct clinical evidence, I prefer a dose of azithromycin 250 mg 3 times/week for COPD exacerbation prevention, considering the very high tissue and cellular penetration where the drug exerts its effects, the long half-life, dose-dependent hearing loss, and GI adverse effects, data in cystic fibrosis, and medical legal concern over the rare cardiovascular effects. There is one study showing that this dose works for cough.[59] The long half-life, dose-dependent hearing loss, and GI adverse effects, data in cystic fibrosis, and medical legal concern over the rare cardiovascular effects.

Adverse Effects

The most common adverse effects of macrolides are GI, principally diarrhea; clarithromycin is also associated with a metallic taste.[57,62] Macrolides can function as pro-kinetic agents by increasing the activity of a pro-motility intestinal hormone, motilin. Erythromycin, clarithromycin, and to a lesser extent azithromycin affect motilin, promoting diarrhea.[63] Another important mechanism of diarrhea is changes in gut microflora, for which all macrolides are potential contributors. In the COLUMBUS study, diarrhea was reported in 19% of subjects versus 2% in the placebo group.[56] However, a study by Simpson et al[64] showed a lower rate of diarrhea in COPD subjects receiving azithromycin 250 mg daily than those on placebo. Dose-related sensorineural effects leading to hearing loss can occur with all macrolides and are usually mild and reversible, but sometimes this can be irreversible. This may be particularly important to consider and monitor in patients who have other risk factors for hearing loss. An animal study indicated that the sensineural effects were due to dysfunction of the outer hair cells of the inner ear.[65]

Concerns over the potential cardiovascular effects of azithromycin have become a topic of much discussion in the management of COPD. Macrolides can cause a prolongation of the QTc interval by blockade of the rapid delayed rectifier potassium current conducted by the human ether-a-go-go-related gene encoded potassium channel.[66] A prolonged QTc may be associated with an increased risk of ventricular arrhythmia (ie, Torsades de pointe). In the azithromycin package insert[57] it is noted that "in comparison to chloroquine alone, the maximum mean (95% upper confidence bound) increases in QTcF were 5–10 ms, 7–12 ms, and 9–14 ms with the co-administration of 500 mg, 1,000 mg, and 1,500 mg azithromycin, respectively."[57] The study was conducted in 113 healthy subjects and suggests a dose-dependent effect of azithromycin on the QTc interval. A 2012 FDA guidance on drugs that can be pro-arrhythimic reports that an increase in the QTc of 5 ms should lead to additional studies evaluating potential cardiac effects.[67] Thus, the effects of azithromycin based on a 5-ms increase in QTc would indicate that there is some potential to have cardiovascular adverse effects. Oral azithromycin has an oral bioavailability of ~30%, subsequently intravenous azithromycin would yield much higher concentrations and may have a greater risk of cardiac events in the hospitalized setting, where this route of administration might be employed. To my knowledge, the difference in potential cardiac effects of azithromycin between oral and intravenous has not been elucidated. Intravenous erythromycin has been shown to have a higher risk of QTc prolongation than oral administration.[68]

The potential adverse cardiac effects of azithromycin came under FDA scrutiny in 2012, and in 2013 the warn-

ing in the package insert was updated. This change in the package insert was largely in response to a retrospective study in the Tennessee Medicaid population[69] and by an FDA review that indicated there is a risk of cardiac events associated with azithromycin.[70] The added warning in the package insert is as follows: "Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and Torsades de pointes, have been seen with treatment with macrolides, including azithromycin. Cases of Torsades de pointes have been spontaneously reported during post-marketing surveillance in patients receiving azithromycin. Providers should consider the risk of QT prolongation, which can be fatal when weighing the risks and benefits of azithromycin for at-risk groups including: 1) Patients with known prolongation of the QT interval, a history of Torsades de pointes, congenital long QT syndrome, bradyarrhythmias, or uncompensated heart failure patients on drugs known to prolong the QT interval; 2) patients with ongoing pro-arrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically important bradycardia; and 3) in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents."[57]

Data concerning the potential cardiac effects associated with azithromycin include animal studies, published case reports, prospective studies for clinical use of macrolides for acute infections and anti-atherogenesis effects in coronary artery disease, retrospective studies using health care databases, the FDA's spontaneous Adverse Event Reporting System,[71] and studies of chronic azithromycin for COPD. Animal studies indicate that azithromycin has a lower potential for prolonging the QTc than erythromycin and clarithromycin. At much higher concentrations than achieved clinically in humans, it was found in animals that azithromycin exhibited either a very lowor no potential for QTc prolongation.[72-76] One study indicated that, even though azithromycin prolonged QTc at very high concentrations, ventricular arrhythmias did not occur because of the manner in which the drug affected cardiac conduction.[74] Bradycardia was reported with very elevated concentrations of azithromycin.[74]

In addition, macrolides like clarithromycin and erythromycin are considered to have an increased risk of causing Torsades de pointes because of metabolic liability, ie, these macrolides are strong inhibitors of CYP3A4, a metabolizing enzyme responsible for the metabolism of many drugs. Azithromycin has low metabolic potential.[68]

Case reports have been few and sporadic; this is notable considering the $>$ 40 million prescriptions for azithromycin in 2011.[70,77] Data from the FDA Adverse Event Reporting System showed that, between 2004 and 2011, there were a total of 203 reports of azithromycin-associated QT prolongation, Torsades de pointes, ventricular arrhythmia, and sudden cardiac death resulting in a total of 65 fatalities.[78] This time frame included the United States and European databases and likely reflects hundreds of millions of patients who received azithromycin.

Several retrospective studies using health care databases have been published regarding potential azithromycin-associated cardiac effects.[69,79-82] Studies in the Tennessee Medicaid population[68] and the Veterans Administration health system[80] both reported an increased risk of cardiac events with azithromycin compared to amoxicillin; the latter study also showed that levofloxacin was associated greater cardiovascular risks.[80] In the Medicaid study, although the authors attempted to adjust for cardiac risk factors, the majority of the measures that may have affected outcomes in these subjects were worse in those persons receiving azithromycin.[68] In both of these studies, the increased cardiac events were more likely to occur in the first 5 d. One would expect that, if it were a function of tissue concentrations in cardiac tissues, the effects would be more likely to occur $\geq$1 week into therapy as the drug accumulated due to its 70 h half-life. In a retrospective study in patients hospitalized for community-acquired pneumonia, the overall 90-d mortality was lower in those who received azithromycin.[82] There was either no difference in overall cardiac events or a slight increase of myocardial infarctions with azithromycin in that study. Two large European retrospective studies, one in Denmark and another using various databases, found no difference in cardiac events between azithromycin and amoxicillin.[79,81] Both studies also found that the risk was greater for azithromycin and amoxicillin than no antibiotic therapy. Although these studies tried to account for other cardiac risk factors, the reality is that quinolones and macrolides are more likely to be used in sicker patients than amoxicillin and in patients not receiving antibiotics.

In a meta-analysis that included 12 prospective placebo-controlled studies (n = 15,558 subjects), 4 of the studies were of azithromycin for acute infections and 5 studies assessed potential benefits of macrolides against *Chlamydiae*-related artherogenesis in subjects with coronary heart disease.[83] The latter represents a population at high risk of drug-related cardiovascular events. No increased risks for total mortality or cardiovascular events associated with azithromycin therapy compared with placebo were found. These prospective studies may represent the strongest evidence for the lack of significant cardiac risks associated with azithromycin.

Several prospective studies have been conducted regarding the use of chronic azithromycin to prevent COPD exacerbations, each of these studies excluded patients with known prolonged QTc and significant cardiac risk factors.[55,56] None of these studies found an increased risk of cardiac events, although they had excluded high-risk patients.

Table 5. Key Points About Leukotriene Modifiers (Montelukast, Zafirlukast, Zilueton)

Indication	Asthma, allergic rhinitis (montelukast only); not effective in COPD
Mechanism	Leukotriene receptor inhibition (montelukast, zarfirlukast), primarily LTD4 (anti-inflammatory)
	Lipoxygenase inhibition leading to decreased production of leukotrienes (LTB4, LTC4, LTD4, LTE4) (anti-inflammatory)
	Symptom relief, bronchodilation, decrease asthma exacerbations, relief of allergic rhinitis symptoms (montelukast); additive to inhaled maintenance medications in asthma
Clinical role	As maintenance monotherapy in mild asthma and add-on to inhaled maintenance medications in moderate-to-severe asthma
Dosing	Montelukast 10 mg, once daily
	Zafirlukast 20 mg, twice daily on empty stomach
	Zileuton 600 mg, 4 times daily or 1,200 mg twice daily for extended-release product
Key drug interactions	Zafirlukast with warfarin, zafirlukast with erythromycin; zafirlukast and zileuton with theophylline
Main adverse effects (dose dependent)	All 3 agents generally well-tolerated, gastrointestinal effects (infrequent), infrequent central nervous system effects including mental status changes, monitor liver function tests for zileuton

In all likelihood, the intense scrutiny of cardiovascular events related to azithromycin in COPD is disproportionate to the actual risk associated with the drug. Likely, many millions of dollars have been spent on electrocardiograms and interpretations, and numerous COPD patients have not received azithromycin because of the FDA warning. A meaningful study is needed, perhaps only possible using large health care databases, as a placebo study is likely not feasible, to evaluate the overall potential mortality benefits as well as cardiovascular risks of azithromycin specifically in COPD patients. One might expect that the decrease in exacerbations with azithromycin has the potential to impact mortality if studied in large enough a population. The upcoming proposed PCORI study comparing azithromycin to roflumilast in COPD may provide additional insight.[5]

Leukotriene Modifiers

The leukotriene modifiers currently available in the United States are montelukast, zarfirlukast, and zileuton; the first 2 agents are receptor antagonists, and the last is an inhibitor of the enzyme 5-lipo-oxygenase that is responsible for the production of leukotrienes (Table 5). These agents have been cleared for use with asthma in the United States for nearly 20 years; more recently, the FDA denied over-the-counter status for montelukast in 2014. All 3 are cleared for persistent asthma; montelukast is cleared for the acute prevention of exercise-induced bronchoconstriction as well as for the treatment of allergic rhinitis, making it an attractive agent for use in patients with both allergies and mild asthma.[84] Intravenous montelukast has been shown to be beneficial in acute asthma, but this is product is not available.[85]

GINA 2017 recommends leukotriene modifiers in the treatment of mild asthma as an alternative therapy, and for moderate or severe asthma, these agents can be given in combination with other therapies such as ICS/LABA.[23] The GOLD 2018 COPD guideline states that leukotriene modifiers have been inadequately studied in COPD to support use.[2] A meta-analysis of 7 studies evaluating the different leukotriene modifiers in stable COPD found modest or no benefits of these agents.[86]

Mechanism of Action

Leukotrienes (LTC4, LTD4, LTE4, and LTB4) are potent mediators derived from arachidonic acid through the 5-lipoxygenase pathway.[87] The cysteinyl leukotriene type 1 (CysLT1) receptor is localized in the human airways and synthesized by a variety of cells including mast cells, eosinophils, and basophils. Cysteinyl-LTs are very potent endogenous bronchoconstrictors. LTC4, LTD4, and LTE4 have similar contractile activity on human airway smooth muscle. Blockade of the leukotrienes leads to modest bronchodilation with an onset of action of 1–2 h. Montelukast and zafirlukast are selective leukotriene receptor antagonists that specifically block the CysLT1 receptor, principally affecting the binding of LTE4 to the CysT1 receptor.[87] Because zileuton blocks the leukotriene pathway at the level of 5-lipoxygenase, additional effects occur on LTB4 as well as on the other leukotrienes, which translates into slightly greater effects on FEV_1 than receptor blockers. (15% vs 10–12%) Leukotriene modifiers have also been shown to decrease blood eosinophils.

Leukotriene modifiers are effective in preventing asthmatic responses induced by allergen challenge, exercise, and aspirin.[87,88] Leukotriene modifiers also reduce both early- and late-phase reactions to inhaled antigens. Because leukotriene modifiers are administered systemically, it is possible that these agents may be delivered to some areas of the lung that can't be reached with inhaled agents, and therefore they may have additional pharmacologic effects. In a study of asthmatics, using high-resolution computed tomography, montelukast decreased distal air trapping more than the ICS/LABA, but airway remodeling was no different.[89]

Aspirin-sensitive asthma occurs in ~5% of asthmatics, especially those with nasal polyps such as those seen in Samters Triad.[90] In some patients with this condition, fatalities can occur when aspirin, non-steroidal anti-inflammatory drugs (NSAIDS) like ibuprofen, or cyclo-oxygenase inhibitors-2 (COX-2) are administered. The pathophysiology of this condition is somewhat unclear. Aspirin, NSAIDS, and to a lesser extent COX-2 inhibitors inhibit the cyclooxygenase pathway and shunt arachidonic acid through the 5-lipoxygenase pathway to produce more leukotrienes, promoting bronchoconstriction.[90] Although leukotriene modifiers appear to modulate the effects of aspirin in aspirin-sensitive asthmatics, the risk of severe bronchoconstriction in this setting may be too great. In the aspirin-sensitive asthmatic, desensitization may be a better option if aspirin is needed, such as for cerebro- or cardiovascular diseases. Although COX-2 inhibitors are more selective than aspirin or NSAIDs and are therefore less likely to cause bronchoconstriction in this patient type, these agents are not totally selective and do have some risk of causing bronchoconstriction.

Treatment effects of leukotriene modifiers include improvement in asthma symptom scores, as-needed β-agonist use, and peak expiratory flow measurements.[88,91] These effects can occur within the first 24 h, but longer courses are needed to assess the clinical benefits due to the variability of asthma symptoms and air flow obstruction. Leukotriene modifiers can provide additive effects of FEV_1 and symptoms when used as an add-on agent with ICS and ICS/LABA therapies for asthma.[92,93]

Pharmacokinetics and Pharmacodynamics

The bioavailability of zafirlukast and zilueton is > 90%, whereas montelukast is only 40% absorbed when administered orally.[94-97] The oral bioavailability of montelukast[95] and zileuton[97] is not significantly affected by food, whereas the absorption of zafirlukast is decreased by nearly 40% when taken with food.[96] All of these agents are > 90% bound to plasma albumin. Each of these agents is extensively metabolized by the liver, and metabolites are less active than the parent drugs. Zafirlukast is metabolized through the cytochrome CYP2C9 pathway, montelukast by CYP2D8, and zileuton by CYP1A2, CYP2C9, and CYP3A4. Zafirlukast inhibits CYP3A4 and CYP2C9. Patients with mild-to-moderate hepatic insufficiency and clinical evidence of cirrhosis had decreased metabolism of montelukast resulting in ~40% higher area under the serum concentration curve.

Regarding pharmacodynamics, a study of asthma patients compared different doses of zafirlukast (5, 10, 20, 40, or 100 mg every 12 h) prior to LTD4 challenge.[84] For patients receiving 10, 40, or 100 mg, the LTD4 bronchoprovacation PC20 FEV_1 increased > 10-fold, showing a slight dose dependence. A dose-ranging study of montelukast in a group of adult asthmatics found that 10 mg once daily was as effective as 200 mg daily.[98] For zileuton, no differences were found between doses of 400 mg and 600 mg 4 times/d.[99]

Drug Interactions

Among the 3 leukotriene modifiers, montelukast the fewest drug interactions whereas zafirlukast and zileuton are more inclined to drug interactions. Co-administration of multiple doses of zafirlukast (160 mg/d) to steady-state with a 25-mg dose of warfarin (CYP2C9 substrate) in healthy volunteers resulted in a significant increase of one third in the mean prothrombin time.[96] Both zafirlukast and zileuton can also increase blood concentrations of theophylline. Co-administration of zafirlukast with erythromycin resulted in decreased mean plasma concentrations of zafirlukast due to a 40% decrease in zafirlukast bioavailability.[96]

Dosing

Zileuton was originally dosed 4 times/d, but as a controlled-release tablet it can be dosed twice daily.[97] Zafirlukast is administered twice daily 1 h before or 2 h after meals, making it difficult for patients to adhere to the protocol.[96] For prevention of exercise-induced asthma, montelukast is dosed 2 h prior to exercise, and if taken daily as a maintenance medication, additional doses are not recommended prior to exercise.[95] Although it is recommended to administer montelukast in the evening to target night-time/early morning symptoms, it is reasonable to take it in the morning if it is more convenient for the patient.

Adverse Effects

Adverse events with these medications are uncommon and are usually mild, including headache, dyspepsia, nausea, and pharyngitis.[100,101] Reversible elevations in liver transaminase enzyme can occur, and this is most likely with zileuton, where monitoring of liver function tests at baseline and periodically is recommended. Patients can be instructed to take zileuton with food to ameliorate GI adverse effects.

Patients may also experience generalized flu-like symptoms, sleep disturbances (including dream abnormalities and insomnia), hallucinations, and drowsiness.[100,101] Rarely, these agents are associated with a condition called Churg-Strauss syndrome (eosinophilic granulomatosis), which can be serious if not identified. Rash, worsening asthma, and neuropathy can occur with Churg-Strauss syndrome.

The FDA first alerted health care professionals about a possible association between the use of leukotriene inhibitors and neuropsychiatric events in 2008 and then added

Table 6. Key Points About Mucoactive Agents (Guaifenesin, N-acetylcysteine, Carbocysteine)

Indication	Not FDA-cleared specifically for COPD or asthma
Mechanism	Guaifenesin is an expectorant via stimulation of the cholinergic pathway to promote airway particle clearance N-acetylcysteine and carbocysteine are antioxidants cleaving disulfide bonds in mucus
Clinical role	Aid in expectoration of mucus in COPD, although efficacy is controversial for guaifenesin; N-acetylcysteine and carbocysteine can decrease COPD exacerbations
Dosing	In general, doses are high, eg, guaifenesin 600 mg twice daily and N-acetylcysteine 600 mg twice daily
Key drug interactions	None
Main adverse effects (dose-dependent)	Minimal adverse effects, eg, possible excess thinning of sputum

information to the package inserts in 2009.[102] These events include agitation, aggression, dream abnormalities and hallucinations, depression, sleeplessness, irritability, suicidal behavior (including suicide), and tremor. While the precaution was extended to all leukotriene modifiers, the primary concern was with montelukast due to its widespread use in adult and pediatric patients. Studies of neuropsychiatric effects from monteluakst have shown variable findings. Ali et al showed no significant effects in a case-control study, whereas a retrospective study using the Netherlands and World Health Organization pharmacovigilance databases found that montelukast can increase the risk of neuropsychiatric abnormalities.[103] In the latter study, nightmares were more common in children taking montelukast. Depression was reported most frequently in the whole population to the global database, whereas aggression was reported the most in children.

Expectorants/Mucolytics

Patients with asthma and COPD invariably exhibit characteristics of excessive airway mucus secretion. Drugs that alter the viscoelasticity of mucus and promote clearance of secretions from the airways are characterized as mucoactive and include expectorants such as guaifenesin, mucolytics (N-acetylcysteine), or mucokinetics (inhaled β2 agonists).[104-106] Among numerous studies of these agents in airway diseases, effects on mucociliary clearance have shown conflicting evidence. However, these agents are widely used by many prescribers. In a recent survey in the United Kingdom, guaifenesin was prescribed by 90% of responding pulmonologists, who reported using it in 20% of their COPD patients, and they felt it was most effective in moderately severe COPD as part of other treatments.[107] The use of mucolytics like N-acetylcysteine and expectorants is likely influenced by the wide safety margin, over-the-counter availability, and low costs (Table 6).

For normal mucociliary function, the surface liquids have to exhibit certain chemical and physical characteristics to interact with cilia for mucus clearance and to serve as a barrier.[108] Airway mucus is secreted by goblet cells found in the superficial mucosa and the mucous glands in the submucosa. Goblet cells are most dense in larger airways, decreasing in number further into the airways, and eventually are non-existent at the terminal bronchioles. In the healthy mucus layer, MUC5B and MUC5AC (mucin polymers) are the framework of the mucus gel in the airways and are normally well hydrated. The mucins can serve to prevent barrier dehydration, present ligands to sequester pathogens, and contain host-protective substances. The periciliary layers, which consist of mucus-producing glands and cilia on the epithelial surfaces of the airways help promote movement of mucus and keep the lungs free of debris and inflammatory substances. In a healthy person, the periciliary layers are well hydrated and exhibit effective lubricant activities, allowing the mucus layer to flow with low friction. Rhythmic beating of the respiratory cilia also enables the mucociliary elevator that transports mucus and liquid as well as inhaled particles and pathogens from distal to proximal airways to be expectorated or swallowed.

About 20–50% of COPD patients, especially current smokers, meet the definition of chronic bronchitis, which consists of a productive cough for at least 3 months for the last 2 years.[2] The pathophysiological consequences of mucus hypersecretion and slowed mucus clearance are airway obstruction, air flow limitation, and impairment of gas exchange.[108] The primary mechanisms responsible for excessive mucus production in chronic bronchitis are the overproduction and hypersecretion by goblet cells and the decreased elimination of mucus. Alterations in mucin polymers occur with chronic bronchitis and long-term smoking. The levels of the gel-forming mucins, MUC5AC and MUC5B, are elevated in the airways and sputum of individuals with chronic respiratory diseases, which can contribute to the viscoelastic properties of mucus. In chronic bronchitis, the mucus can contain high levels of protein and other types of debris, making it heavy and more difficult to move along the periciliary layers. Expectorated mucus (ie, sputum) tends to be thick and tenacious in some patients, making it difficult to bring up and eliminate.

Mechanism of Action

A mucoactive drug is defined as an agent that can modify mucus production, secretion, composition, or interaction with the mucociliary epithelium.[104,108] Mucoactive drugs can induce cough or increase the volume of secretions (expectorants); mucolytics reduce the mucus viscosity; and mucokinetic drugs such as β2 agonists, which increase the mucus mobility and transportability. The predominant agents used are N-acetylcysteine, carbocysteine, and guaiafenesin (glyceryl guaiacolate). Although inhaled β2 agonists are typically not prescribed for their mucokinetic properties, they are used widely and therefore are likely promoting mucus clearance in patients. Nebulized hypertonic saline (7%), a mucoactive therapy shown to be efficacious in cystic fibrosis, is associated with worsened lung function in COPD patients.[109] Similarly, dornase-alpha (Pulmozyme, Genentech, San Francisco, California), an inhaled enzyme drug that is effective in cystic fibrosis, has been shown to worsen outcomes in COPD patients.[110]

Expectorants like guaifenesin are defined as medications intended to improve the ability to expectorate purulent secretions. Expectorants are now taken to mean medications that increase airway water or the volume of airway secretions, including secretagogues that increase the hydration of lumen secretions, such as nebulized hypertonic saline.[104] Expectorants do not alter ciliary beat frequency or mucociliary clearance. Guaifenesin is commonly used for acute respiratory tract infections in otherwise healthy persons and has no mucolytic action, but it may reduce bronchial sputum surface tension. One potential mechanism is stimulation of the cholinergic pathway to increase mucus secretion from the airway submucosal glands. It can be ciliotoxic when applied directly to the respiratory epithelium. Some studies have shown positive effects of guaifenesin in patients with bronchitis,[111-113] whereas others have been negative.[114] Thomson et al studied the effect of guaifenesin on the clearance of radioactively tagged particles from the human lung and found in a double-blind study that 600 mg of the drug significantly sped airway particle clearance in 7 bronchitic subjects, but not in normal volunteers.[111] Chodosh found that guaifenesin reduced the stickiness of mucus.[113] Another study found that guaifenesin impaired ciliary beat frequency,[115] whereas in another study, a single 1,200-mg dose of Mucinex (Reckitt Benckiser, Berkshire, United Kingdom) did not have a positive effect on mucus clearance in persons with respiratory tract infections.[116]

N-acetylcysteine and carbocysteine work by two mechanisms: anti-oxidant and cleaving of disulfide bonds in mucus.[105] Given that oxidative stress associated with the chronic inflammatory state is crucial to the pathogenesis of COPD, antioxidant therapy may be of benefit in COPD. N-acetylcysteine also reduces by hydrolysis disulfide bonds and sulfhydryl bonds that link together mucin polymers, thereby reducing sputum viscosity. This is usually accomplished by free thiol (sulfhydryl) groups, which hydrolyze disulfide bonds attached to cysteine residues. N-acetylcysteine is a precursor of L-cysteine and reduced glutathione, which reduce the cellular levels of oxidative stress and the production of reactive oxygen species. Carbocysteine, which is used outside the United States, is a thiol derivative of L-cysteine with in vitro free radical scavenging and anti-inflammatory properties. To exert some effects in the lungs, concentrations of N-acetylcysteine and carbocysteine have to achieve adequate concentrations in bronchial epithelium or in epithelial lining fluid.[117]

A number of studies investigating the potential benefits of N-acetylcysteine and carbocysteine in COPD have yielded variable results. The Bronchitis Randomized On N-acetylcysteine Cost-Utility Study (BRONCUS) was the largest trial of N-acetylcysteine in COPD.[118] More than 500 subjects were randomized to N-acetylcysteine 600 mg daily or placebo, and they were followed for 3 y. There were no differences in FEV_1 decline over time or in health-related quality of life between the 2 groups. There was also no overall difference in the number of exacerbations. However, in a post hoc analysis, those without ICS ($\sim$30% of the entire group) had a significant reduction in exacerbations with N-acetylcysteine compared to placebo.

The more recent High-Dose N-Acetylcysteine in Stable COPD (HIACE) study enrolled 120 stable COPD subjects who were randomized to receive a higher dose of N-acetylcysteine, 600 mg twice daily, or placebo daily for 1 y.[119] Subjects in the N-acetylcysteine group had decreased small airway resistance compared to the placebo group. In addition, the N-acetylcysteine group had a statistically significant increase in FEF_{25-75}. The mean exacerbation frequency in the N-acetylcysteine group was lower (0.96/y) compared to the placebo group (1.71/y), although this was not statistically different.

Carbocysteine, which is not available in the United States, has been studied in China in subjects with COPD. In the PEACE study, $>$ 700 subjects with at least 2 exacerbations within the last 2 y received either carbocysteine 500 mg 3 times/d or placebo, with the primary end point of exacerbation rate over 1 y.[120] The number of exacerbations per patient per year declined significantly in the carbocysteine group compared with the placebo group (relative risk: 0.75). Unlike the BRONCUS study, there were no significant interactions between the primary end point and COPD severity, smoking, and use of ICS.

In a Cochrane systematic review of 30 randomized studies in 7,436 subjects, mucolytics reduced the risk for exacerbation of COPD by 17% compared with placebo.[121] This translates to a number needed to treat of 6 to prevent 1 more exacerbation. They had an even more profound effect in reducing the number of days with disability per

month. However, mucolytics did not improve lung function or the risk for death. There was no overall effect on lung function or increase in adverse effects from the medications.

The β_2 agonists can increase mucociliary clearance, functioning as mucokinetic agents. Specifically, β2-agonists increase the airway ciliary beat frequency to help with the upward movement of mucus to be expelled or swallowed.[104] In addition, the bronchodilatory effects of these agents may play a role in helping promote the clearance of mucus from the airways. When nebulized, the increased hydration may also help promote mucociliary clearance.

Pharmacokinetics and Pharmacodynamics

Guaifenesin pharmacokinetics have been determined in adults.[122,123] After oral administration, peak blood levels occur in $<$ 1 h, and the drug exhibits a short-half half-life of 0.8 h over the range of 600–1,200 mg. Following multiple-dose oral administration of an immediate-release formulation, steady-state was rapidly achieved, although a pharmacokinetic steady state does not necessarily define the maximum effectiveness of a drug therapy. With oral administration, guaifenesin is primarily metabolized, and β-(2-methoxyphenoxy)-lactic acid is the major urinary metabolite.

N-acetylcysteine is rapidly absorbed after an oral dose of 600 mg with a peak after 1 h,[124] and it is quickly metabolized to cysteine. The plasma half-life has been reported to be 2.5 h, and no N-acetylcysteine is detectable 10–12 h after administration. It has been estimated that the oral bioavailability of the intact N-acetylcysteine molecule is ~10%.

Dosing

The standard dose for guaifenesin as an expectorant in the COPD patient is 600–1,200 mg daily, taken with liberal amounts of fluids to also promote mucus hydration. A meta-analysis indicated that higher doses are more effective than lower doses of guaifenesin.[125]

Drug Interactions

There are no known drug moderate or major interactions with guaifenesin or oral N-acetylcysteine.

Adverse Effects

Side effects are uncommon with N-acetylcysteine and guaifenesin, but there is the potential that mucolytics or expectorants may cause mucus to be too thin, making expectoration less effective. No serious adverse events have been reported in clinical trials involving N-acetylcysteine. Some data from rat studies suggest that, as an anti-oxidant, N-acetylcysteine, may increase cancer risk.[126] There is inadequate evidence to withhold these agents in COPD patients because of this concern. At higher doses, guaifenesin is emetogenic.

Summary

Each of the oral agents available for the maintenance therapy of obstructive lung diseases have unique pharmacologic mechanisms, and most work through inflammatory pathways. PDE inhibitors and theophylline both affect cAMP to exert modest bronchodilation and significant anti-inflammatory effects. Leukotriene modifiers affect the lipoxygenase arm of the arachidonic pathway to exert anti-inflammatory and mild bronchodilatory effects. Several of these oral agents undergo hepatic metabolism, which creates the potential for drug interactions that can be significant for agents like theophylline and zileuton. Usually these oral agents are part of the patient's drug therapy regimen, and they are rarely used alone for the treatment of obstructive lung disease, with the exception of leukotriene modifiers in some mild asthmatics. Side effects can be a significant issue with theophylline and roflumilast in some patients, especially upon initiation of therapy, but these effects tend to wane in within 1–2 weeks after starting. The efficacy and safety of chronic azithromycin in COPD and asthma continues to be defined. Cardiac adverse effects of azithromycin have been reported, but they are likely overemphasized for the treatment of COPD, especially considering the positive benefits and low cost. Some mucoactive agents may play a role for some COPD patients to aid with secretions and risk of exacerbations.

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Discussion

Peters: We were asked to write an editorial[1] on Rick Albert's paper[2] on azithromycin in COPD. One of our biggest criticisms was in the online supplement. The data demonstrated that the major effect was in subjects with mild-to-moderate COPD and not in subjects with severe COPD. As clinicians we consider adding a macrolide in patients with severe COPD exacerbations or in patients with concomitant bronchiectasis; we don't add it to patients with mild-to-moderate disease. Do we have additional data to show that macrolides benefit patients with severe COPD?

Pleasants: That's a good question. One study[3] showed, along with the Albert study,[2] that COPD subjects with mild to moderate disease had greater benefits with azithromycin than those who had more advanced disease.

Donohue: I'd like to ask Mike [Wechsler] a question. Many years ago Richard Martin was telling us about an experience at National Jewish where azithromycin or clarithromycin was steroid sparing. They did bronchoscopy and saw a ciliocytopthoria, which is a marker of mycoplasma infection. I always thought that was terrific because those are the kind of asthmatic patients I had seen, and I had done that in about every asthmatic patient who came to me on steroids. Has that been replicated or has there been follow up to that?

Wechsler: In the 90s there were a few studies by Monica Kraft and Richard Martin[4] that demonstrated that a subset of subjects with asthma had evidence of mycoplasma or chlamydia in their airways. And for those people, giving chlarithomycin was beneficial in terms of improvement in symptoms and FEV_1. There was a study that we published as part of the Asthma Clinical Research Network called the Macrolides In Asthma (MIA) study.[5] In that study we did bronchscopy and weren't actually able to identify a significant proportion of subjects who had evidence of mycoplamsa or chlamydia. That study was a negative study, mostly due to failure to identify a substantial number of patients the way we did that. Since that time there have been a few updates. One is a study that Homer Boushey[6] from UCSF led was an airway microbiome study. They demonstrated that the airways of asthmatics have abundant microorganisms, and in a cohort of milder subjects there was evidence of significant organisms including those we wouldn't expect like fungal organisms, ones we would see in cystic fibrosis and others. That wasn't a treatment trial. There was recently presented at the ATS meeting a large study in which subjects were given azithromycin over the course of a year and they demonstrated a 40% reduction in asthma exacerbations. They did a subgroup analysis to see if it was primarily in the subjects who had neutrophilic asthma, as would be expected,[7] and it turned out that subjects with eosinophilic asthma were more likely to have a benefit. I'm going to be talking about biologics shortly, and if you think of the cost of the biologics of $30,000+ vs the cost of azithromycin for a year and they get about the same 50% reduction in exacerbations. That was a study from Australia[8] that was recently published. They randomized 1,000 subjects to receive azithromycin 500 mg 3 times a week for 48 weeks and azithromycin reduced severe asthma exacerbations by 41% compared to placebo, and in eosinophilic asthma it reduced asthma exacerbations by 56%. While diarrhea was more common in the treatment group at 34 vs 19%, azithromycin-treated subjects had fewer respiratory infections 20 vs 36%. So the conclusion was that across the board there were significant reductions in asthma exacerbations in subjects treated with azithromycin. This is somewhat different than the AZALEA trial[9], which was a negative study.

Peters: Interesting, since the AZISAST study[10] didn't find the same results. That study found no benefit in the overall group; yet, when they did the subgroup analysis meeting the criteria for neutrophilic asthma (negative eosinophils in the peripheral blood with a low F_{ENO}), they found significant benefit. For years, we have been trying to find the role of Mycoplasma in asthma. We have instilled both Mycoplasma organisms and Mycoplasma toxin (CARDS toxin) into baboons. Both the toxin and the organisms result in an asthma-like response (eosinophils with occasional mucus plugging) in this non-allergic primate model. This research has been recently published.[11] I am not sure how to clinically identify these patients. When we send nasal and oral swabs to the hospital lab (which looks for Mycoplasma using a PCR method (called BioFire), the assay is negative; yet when we run specimens in our research lab we find evidence of Mycoplasma or CARDS toxin. I think it is a matter of how sensitive the commercial assays are.

Rubin: We have been studying macrolides for 30 years and were the first to use them in CF. In fact I co-edited the book[12] on the use of immunomodulatory agents and antimicrobials. There are no later data that suggest clearly that Mycoplasma infection plays a role in macrolide efficacy in diffuse panbronchiolitis or CF, and I don't believe, in COPD. There are data[13] looking at non-antimicrobial macrolides, including EM900, developed in Japan. There's another product that was developed by Zambon, and all of these have significant immunomodulatory effects. Primarily through its effects on the extracellular-regulated kinase, which is thought to be the primary effect. Which would strongly implicate both neutrophilic and also eosinophilic in that IL-13, a major driver of mucus hypersecretion in asthma, is completely steroid resistant but it is sensitive to macrolides.It's still an evolving issue. In fact, on Saturday I'm giving a talk on this at another conference on another continent. But the data seem to suggest it's primarily immunomodulatory rather than antimicrobial that you see the same effects with non-antimicrobial macrolides. That low dose and less frequent is effective, and in fact you seem to lose some of these

effects if you use it at the regular antimicrobial dosages. When the studies were done in CF, surprisingly clarithromycin did not have a benefit.[14] We were initially interested in the use of clarithromycin and the initial studies were funded by Taisho who developed it rather than by Pfizer. I think that's why the CF group has switched over entirely to using azithromycin.

***Hess:** Since many of the readers of the Journal are respiratory therapists I wanted to clarify that your comments about N-acetylcysteine apply to oral administration and not inhaled. Is that correct?

Pleasants: I didn't specify. My observation is that it is used uncommonly in the inhaled route. Does anybody else want to speak to that?

***Hess:** Correct me if I'm wrong, but I don't know of any high level evidence that supports their use by the inhaled route.

Rubin: There is no evidence for the inhaled route. There was a large study[15] funded by Zambon, which makes Fluimucil, the most commonly prescribed oral N-acetylcysteine used as a mucolytic in Europe. It included over 500 subjects with COPD. They followed these subjects for 3 years and there was no difference whatsoever in exacerbations or rate of decline in lung function in the placebo compared with the N-acetylcysteine (Fluimucil) groups.

Peters: I need to chime in because there is one study[16] from the surgery department in Dallas that used to perform lobectomies in patients who had mucoid impactions. We have experience instilling N-acetylcysteine combined with albuterol and saline directly through the bronchoscope and it has been very effective in dissolving mucus plugs. So when we talk about using N-acetylcysteine by inhalation, the data suggest that there is little or no benefit.

***Hess:** What I was referring to was N-acetylcysteine inhaled through a nebulizer, which I don't think there's strong evidence to support. And I believe that's an important statement - if we all agree - that could come out of this conference, because I think it's still widely used many places, and there is the potential for harm and little evidence to my knowledge.

Peters: I couldn't agree more. We looked at it a while back, of 18 studies 17 were negative and one poorly done study was positive. And yet our surgeons use it post-operatively on an almost routine basis on people with obstructive lung disease.

Pleasants: Inhaled doesn't work.

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