Designing Clinical Trials to Evaluate Mucus Clearance Therapy

Bruce K Rubin MEngr MD MBA FAARC

Mucoactive therapy is meant to improve quality of life by making it easier to breathe and reducing the need for hospitalization and antibiotic therapy. There are a number of challenges when designing a clinical trial to test the effectiveness of potentially mucoactive therapy. These challenges can be categorized as understanding the mechanism of action for the intervention, understanding the disease being treated, and recognizing relevant outcomes that can be accurately measured. Dose, duration, route of administration, and effectiveness of a therapy are all influenced by mechanisms of action. Mucoactive therapy may not change sputum expectoration volume, expiratory airflow, or dyspnea sensation, although these are commonly measured. While clinically relevant outcomes are most informative, surrogate outcomes can be of value. The natural variability of the outcome measure in question in the population being studied must be known in order to design an appropriately powered study. The natural course of the disease being studied and the ability to accurately measure disease severity must be known in order to choose whether studies are conducted during periods of disease stability, at the time of an exacerbation, or immediately following successful therapy for an exacerbation. This information is also critically important in identifying an appropriate control group. These challenges can be met to advance our knowledge and to develop truly effective therapy for mucus clearance disorders. *Key words: outcomes, clinical trials, cystic fibrosis, mucus, sputum, mucociliary clearance, pulmonary function testing, chronic bronchitis, asthma.* [Respir Care 2007;52(10):1348–1358.

Introduction

One of the difficulties in assessing the effectiveness of mucus clearance therapy is selecting relevant outcomes for clinical trials that accurately reflect therapeutic effects, such as mucus transport, or secondary effects of changes in mucus transport, such as the frequency and duration of illness exacerbation, days in hospital, change in pulmonary function, and quality of life (QOL). Distinguishing a placebo effect from the effect of an intervention is critically important if we are to determine the most appropriate use of mucoactive medications or devices. Thus, cause and effect must be clearly established by understanding the intervention's mechanisms of action, the natural history of the disease being studied, and the accurate measurement of the clinical or surrogate outcomes being measured. These data are critically important for appropriately powering the study and interpreting the results.

The most appropriate outcome measurements are different for in vitro, preclinical, and clinical studies and at different stages of the disease process. Depending on the intervention and the disease, it may be more appropriate to study a mucoactive therapy during periods of disease stability or quiescence, during an acute pulmonary exacerbation, or immediately following the successful treatment of an exacerbation of disease. Identifying the correct duration of treatment is critically important to determine an appropriate or sustained effect of therapy. It is important to determine and monitor appropriate adherence to therapy, especially with longer courses of therapy.

For clinical trials an appropriate control group must be identified. This should take into account not only controlling for baseline disease severity, but also for adherence, and with the recognition that many physical interventions can be difficult to mask. For crossover trials, care must be taken to minimize or eliminate crossover treatment effects.

Table 1. Sputum Analysis In Vitro

Measurements that can be made
Rheology (viscoelasticity, yield stress, thixotropy)
Surface properties (adhesivity, wettability, tenacity)
In vitro transportability (cough clearability, mucociliary transportability)
Inflammatory mediators
Drug penetrance into secretions
Drug activation or inactivation
Sputum bacteriology
Biochemical and structural composition of sputum
Requirements
Sputum sampling (difficult for severely debilitated subjects with weak cough)
Special instrumentation
Information generated
Potential mechanism of action
Onset of action
Effective dose
Possible drug interactions
Limitations
Does not give information about how a compound will work in vivo
Sputum is difficult to work with and measurements are not widely available
Healthy subjects and the very young do not expectorate sputum
No information is generated about *mucus*

In Vitro Testing

In vitro testing of mucoactive medications can help to define a primary mechanism of action and to determine the concentration of drug that needs to be achieved in vivo for a desired effect (Table 1).[1] If an intervention has a directly measurable effect on sputum properties (eg, a mucolytic) or on sputum clearability (eg, a mucokinetic medication), and if these changes cannot be demonstrated in vitro, it is unlikely that they will be observed in clinical trials.

Generally, in vitro testing is performed on expectorated sputum. Sputum is a complex and heterogeneous mixture of periciliary fluid, mucus glycoprotein gel, inflammatory cells, effete epithelial cells, inflammatory mediators, bacteria, and saliva.[2] While at this time, no sputum properties have been identified that can convincingly distinguish one pulmonary disease from another, there are sputum characteristics associated with specific disease processes and changes in properties that could suggest the successful application of mechanical or pharmacologic mucokinetic therapy.[3]

Often, in vitro testing can suggest the onset and duration of action for a mucoactive agent, in order to help deter-

Bruce K Rubin MEngr MD MBA FAARC is affiliated with the Department of Pediatrics, Wake Forest University School of Medicine, Winston-Salem, North Carolina.

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Correspondence: Bruce K Rubin MEngr MD MBA FAARC, Department of Pediatrics, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem NC 27157-1081. E-mail: brubin@wfubmc.edu.

mine the appropriate frequency of administration for animal and clinical trials. Therefore, in vitro testing is useful for screening mucoactive medications. However, this does not imply that if an effect is noted in vitro, a similar effect will necessarily be seen with clinical use.

Many patients with chronic airway disease take several different medications and have comorbidities. In vitro testing is also useful for identifying potential medication interactions. For example, in vitro testing suggests that azithromycin can decrease the effectiveness of dornase alfa, while other macrolides do not.[4]

The principal sputum biophysical properties measured in vitro are rheology (viscoelasticity) and cohesivity. The rheology of mucus is its capacity to undergo flow and deformation.[3] An ideal solid responds to a stress with a finite deformation that is recovered after the stress is removed. This stored energy is described by elasticity. An ideal liquid responds to a stress by deforming (flowing) while a stress is applied, and after removing the stress, flow ceases and there is no strain recovery. This energy loss is viscosity. A gel such as mucus initially stores energy like a solid and with continued stress will flow like a liquid. Viscoelasticity must be measured in a rheometer, as the visual assessment of sputum viscosity or density is not accurate.[5]

For mucokinetic agents the most important in vitro tests to conduct are sputum transportability measurements. The mucociliary transportability of sputum is usually measured on the mucus-depleted frog palate.[6,7] In vitro cough transportability can be measured in a simulated cough machine.[8] There is a consensus that sputum surface properties are important for cough transportability,[9,10] but that there is little dependence on viscoelasticity.[11] Sputum cohesivity has been correlated positively with mucociliary transportability,[12] but negatively with cough transportability.[11] Tenacity is the force of separation, and we calculate this as the product of cohesivity and adhesive work. Young's equation allows us to calculate adhesive work between the mucus and epithelial surfaces as $\gamma (1 + \cos \theta)$, where γ is the interfacial tension of secretions in air and θ is the contact angle of mucus on the epithelium. The contact angle measures the wettability of a solid surface, such as the airway epithelium. Interfacial tension at an air-gel interface is most easily measured with the de Noüy platinum ring method.[10] This permits us to directly calculate adhesive work and tenacity. Studies confirm that sputum tenacity is the strongest predictor of in vitro cough transportability.[13]

Animal and Tissue Studies

Techniques for growing a well-differentiated airway epithelium at an air-liquid interface enable some studies to be performed in cell culture systems. For example, the effect of ion or water transport modifiers can be evaluated by the bioelectric properties of airway tissue culture.[14] Cell culture systems are of limited use in assessing mucus clearance (Table 2).

Table 2. Cell Culture Systems

Measurements that can be made
Ion and water transport
Mucin secretion
Induction of inflammation
Biochemical composition of mucus
Requirements
Specialized air-liquid interface culture systems and ability to manipulate these systems
Information generated
Potential effectiveness of mucoregulatory medications, anti-inflammatory drugs
Onset of action
Direct toxicity to cells in culture
Limitations
Artificial system can be difficult to work with
Does not give information about how a compound will work in vivo
No information is generated about *sputum*

Evaluating the efficacy of mucoregulatory agents requires the assessment of mucus secretion in both the normal and the inflamed airway. This can be done using whole animals or airway tissue explants.[15] The secretory cells of the human airway include surface goblet cells and submucous glands, both contributing to the mucus layer. Rodents have a simple airway epithelium usually lacking submucosal glands. Thus, animal studies are generally performed using ferrets, dogs, sheep, or primates. Whole animal studies are particularly valuable for the evaluation of inflammatory mediator release in the inflamed airway and suppression of inflammation-associated hypersecretion by drugs that are biologic response modifiers (Table 3).[16,17] Unfortunately, there are few animal models of chronic airway disease that resemble human disease, and the response of non-human species to drugs can be quite different from that of humans.

Clinical Testing

The purpose of clinical testing is to establish the safety and effectiveness of an intervention (Table 4). Testing should assess the potential toxicity of medications, bioavailability (including ability to penetrate into sputum), pharmacokinetics and pharmacodynamics (which can be different in the airway mucus or sputum than in blood or serum), and patient tolerability of both the drug and the delivery system, as this can influence adherence to therapy.

Table 3. Animal Models

Measurements that can be made
Mucus secretion rate
Mucus transport rate
Radioaerosol clearance
Bioavailability of a medication
Safety and toxicity of a medication
Airway physiology
Histological assessment of epithelium
Requirements
Requires availability of test animals and skill in working with relevant species
Information generated
Response to allergen, irritant, or bacterial challenge
Pharmacokinetics and pharmacodynamics
Minimal effective and maximal tolerated dose of a drug
Limitations
Often there are no truly relevant animal models of human airway disease
Animals can have different physiologic and pharmacologic responses to drugs

Table 4. Questions to Be Answered Before Starting a Clinical Study

Define the disease
Clearly define the patient group
Know the natural history of the disease
Understand co-morbidities
Inclusion and exclusion criteria
Study design
Identify appropriate control group
Parallel group or crossover study?
Washout period for crossover studies
How should the study be masked?
How will adherence to therapy be monitored?
When to study the subjects
Treat during stable disease, during exacerbation, or immediately after exacerbation?
Acute or short-term vs longer-term study?
Should subjects be sick or relatively healthy?
Outcome measurements
Clinical outcomes to study
Surrogate outcomes
Know the variability of outcomes to calculate study power
Identify important safety outcomes
Medication delivery
Dose of medication
Frequency of administration
Route of administration

Whom to Study and When

In clinical trials one of the difficulties is determining the most appropriate population to study. The clinical variability of the disease studied must be taken into account. In patients with slowly changing disease, the duration of therapy and the duration of observation will likely need to be much greater than in those with rapidly progressive disease.[18,19] In many diseases this can be confounded by age, sex, and even by cultural differences (eg, the social acceptability of sputum expectoration). Thus, it is important to define a disease as unambiguously as possible.

One of the more difficult questions to answer is whether testing should be done while the patient is clinically stable, during an exacerbation of lung disease, or immediately following successful therapy for an exacerbation. This is confounded by the lack of clear and uniformly accepted definitions for exacerbation.[20,21] Outcome measures during an exacerbation could include the duration of the exacerbation, need for hospital admission, and rapidity of resolution, but many of these are subjective and might be influenced by medications given concomitantly during the acute illness. Although it is theoretically attractive to begin an experimental intervention immediately following therapy for an exacerbation and using the time until the subsequent exacerbation as a primary outcome measure, identifying the end of an exacerbation is even more difficult and controversial than recognizing when an exacerbation has started. Although for many of these interventions, starting a trial of therapy during a period of clinical stability is more similar to how an established therapy is used clinically, it is likely that subjects with stable disease will have slower progression of clinical measures, thus requiring a greater sample size and longer duration of observation to reach clinical and statistical significance.

Older patients with chronic obstructive pulmonary disease often have confounding diseases, such as cardiac disease or diabetes. Either these diseases or the medications used to control these conditions could affect the outcome of a clinical trial, as could unanticipated medication interactions. Adherence to a medical regimen becomes more difficult if a subject is taking a large number of medications. Difficulty with adherence could be as straightforward as refusal to take medication as prescribed or as complex as ineffective use of medication delivery devices.[22] This has been reported to be a particularly difficult problem when patents use aerosol devices to administer medications—an important issue when using aerosol mucoactive medications.[23]

Because the efficacy of a novel therapy may be best assessed during a clinical trial in a homogeneous population likely to be adherent to a therapeutic protocol, cystic fibrosis (CF) is frequently chosen to be the first group of patients studied when evaluating a novel mucoactive medication or device.[18] However, even CF can be widely variable in presentation and outcome; there are CF transmembrane regulator gene and modifier gene differences, socioeconomic differences that could influence outcomes,[24] and confounding concurrent diseases, such as liver disease

or diabetes. In fact, something as simple—and variable—as different degrees of airway obstruction among patients can influence airway deposition and clearance and thus the efficacy of an aerosol medication.

Identification of an appropriate control population is as important as identifying a uniform patient population to study. Comparisons of a specific therapy to another medication or especially against another airway clearance technique can be very difficult. It is particularly difficult to monitor protocol adherence and to devise appropriate masking (blinding) for evaluating of mucus clearance devices.[25]

Choosing Outcomes or End Points

In clinical trials, power calculations are generally made for a single primary outcome variable. This requires foreknowledge of the most sensitive and specific outcome of interest, as well as sufficient baseline or longitudinal data in a similar population to evaluate measurement variability. There are few large longitudinal studies evaluating any outcome other than pulmonary function testing (PFT), making these the most commonly used tests to evaluate mucoactive therapy. However, lung volume and flow correlate poorly with other measures of mucoactive medication efficacy. Furthermore, in a clinical trial of mucolytic and expectorant therapy for CF, it has been documented that pulmonary function variables are interdependent, and this may lead to inappropriate confidence in the calculated significance of these related outcome measures.[19]

Because of these difficulties, surrogate end points have been used to evaluate mucoactive therapy. These have included both fairly precise measurements of radioaerosol deposition and clearance,[26] as well as theoretically attractive but poorly standardized measures such as QOL. In 2005, an extensive search documented only 16 clinical trials in CF that included QOL outcomes, and none provided any conclusive results concerning QOL.[27]

Other clinical measures that have been used for studies of therapeutic agents in chronic lung disease include days in hospital or days of intravenous antibiotic therapy during the duration of the study, the frequency and duration of exacerbations of pulmonary disease, and the rate of pulmonary function decline over time. Chest imaging has also been used, but simple chest radiographs change slowly with most diseases and thus are insensitive to interventions during the usual duration of a clinical trial. New imaging methods hold promise as appropriate surrogate outcomes, as discussed later in this review.

Finally, changes in the concentration of inflammatory mediators or deoxyribonucleic acid (DNA) in sputum may reflect improved mucus clearance, because expectoration will decrease the burden of pro-inflammatory stimuli in the airway. Pilot studies suggest that the sputum concentration of some mediators associated with neutrophilic inflammation (eg, interleukin-8, DNA, myeloperoxidase) may correlate with temporal changes in PFT results,[28–30] but further research is needed before these can be recommended as reliable outcomes for clinical trials of mucoactive agents.

Clinical Outcome Measures for Short-Term Studies

Pulmonary Function Changes

Spirometry measurements such as FEV_1 are useful for evaluating the acute effects of a bronchodilator medication used to treat asthma, but are insensitive to the acute or long-term effects of mucoactive therapy for any disease. Mucus retention can theoretically have different effects on lung function, depending on the amount and location of mucus. Mucus in small peripheral airways may reduce airway diameter and contribute to airflow obstruction. However, the measurement of forced expiratory airflow does not seem to reflect changes in mucus transport or retention of mucus, as reported in a number of studies.[31–38]

Mucus can also completely obstruct some airways and thus influence static lung volumes and volume of trapped gas. Regnis et al found a weak but significant correlation between mucus transport and the ratio of residual volume to total lung capacity (RV/TLC) ($r = -0.39$) in CF, which suggests that slow mucus transport may lead to gas trapping.[39] It is unlikely that the changes in mucus transport resulting from an intervention can be detected by measurement of lung volumes alone, especially in studies with a relatively small number of subjects.

Imaging Studies

Radiography. Severe mucus retention may cause obstruction of the airway or "mucus plugging."[40] Evaluation of the success of interventions to remove a mucus plug (eg, bronchoscopy, endotracheal suctioning, or chest physiotherapy) is sometimes made by chest radiography. Radiography is insensitive for detecting mucus plugging and is thus insensitive for detecting improvement of mucus plugging. Pham et al[41] studied 8 patients with complete interruption of ventilation to an entire lung and found that chest radiography did not indicate the extent of the obstruction. Bray and colleagues[42] also studied a group of patients with major bronchial obstruction by mucus plugs. The chest radiographs of these patients did not reflect the severity of the airway obstruction, and in some instances were completely normal. Dee et al[43] described 2 quadriplegic patients with clinical and ventilation scan signs of severe mucus plugging. Both of these patients had normal chest radiography.

The inhalation of hyperpolarized helium gas via magnetic resonance imaging may be able to more clearly de-

tect ventilation defects than standard ventilation and perfusion scanning. In a pilot study, 8 subjects with CF had hyperpolarized helium lung ventilation magnetic resonance imaging and performed PFT before and then after inhalation of albuterol, and, finally, after inhalation of dornase alfa with chest physical therapy. After treatment with albuterol there was a small, but significant, decrease in number of ventilation defects ($p = 0.025$), and when this was followed by dornase alfa and chest physical therapy, there was a trend toward *increasing* ventilation defects. As well, in these subjects with CF, hyperpolarized helium magnetic resonance ventilation defects correlated with PFT results.[44]

High-resolution computed tomography can also be used to evaluate ventilation inhomogeneity. In a study of children with CF, the high-resolution computed tomography score significantly correlated with change in exacerbation frequency over 2 years of observation.[45]

What I believe would be most valuable for investigators studying the role of secretions in the pathogenesis of airway disease and the effects of mucus clearance therapy would be a sensitive, high resolution, low-ionizing radiation imaging technique that can quantify the total volume of airway secretions (mucus burden) and be able to distinguish changes in mucus burden after therapy.

Local Tracer Imaging. The transport rate of a tracer that is deposited onto the bronchial mucus layer can be timed and tracheal mucus transport velocity calculated. The tracer bolus is deposited on the large airways through a bronchoscope (being careful not to damage the ciliated epithelium) or via inhalation. The movement of the tracer can be visualized via bronchoscopy or measured via scintigraphy if radiolabeled particles are used. With this technique the tracheal mucus transport velocity of healthy subjects has been reported to be 4.7 ± 1.3 mm/min.[26]

Whole Lung Tracer Imaging. The transport of mucus in the whole lung can be measured by using a tracer that is deposited in the central as well as the peripheral airways. Theoretically, 2 types of tracers can be used: a radiopaque tracer or a radioactive tracer.

Radiopaque tracer is usually introduced as an aerosol, through an endotracheal tube, and is deposited in the airways. The clearance of the tracer is monitored radiographically. The amount of tracer remaining in the lungs after a given time interval is expressed as a percentage of the initial amount. This older technique is invasive, can potentially damage the airways, and uses a relatively high radiation dose, depending on the number of chest radiographs.

To measure mucus clearance with a radioactive aerosol tracer, the tracer aerosol is inhaled and deposits on the airway surface. The amount of radioactive tracer is counted with a gamma camera or scintillation counters. A gamma camera technique has the disadvantage that relatively more radioactivity is necessary, but gamma scintigraphy is best for evaluating the initial deposition pattern so that corrections can be made for deposition in the esophagus or stomach. This also facilitates recording radioactivity in different regions of interest, which allows quantification of the initial deposition pattern and estimation of regional clearance.

In general the transport velocity measured with a tracer technique depends on the site of deposition.[46] The site of deposition can be quantified by calculating the ratio between peripheral and central deposition, or by measuring the retention after 24 hours, representing alveolar deposition. The ratio of peripheral to central deposition and 24-hour retention are equally accurate to quantify the site of deposition. The ratio of peripheral to central deposition has the advantage that it is less time-consuming. The site of deposition of an aerosol in the bronchial tree depends on the inspiratory maneuver and the characteristics of the aerosol. Inspiratory flow is inversely related to the depth of the deposition, such that high inspiratory flow increases central deposition. Particle size influences the deposition pattern; larger particles are deposited more centrally, but there is little effect on mucus transport.[46] The radioactive tracer technique appears to be fairly reproducible in healthy subjects, asymptomatic smokers, persons with chronic bronchitis, and patients with CF.[47]

Volume and Color of Expectorated Sputum

Intuitively, the measurement of expectorated sputum volume might be useful to evaluate the effectiveness of therapeutic interventions meant to improve mucus clearance. However, sputum volume measurements are highly variable and usually inaccurate because of patient reticence to expectorate, inadvertent swallowing of secretions, salivary contamination of expectorated secretions, and variability in cough and thus the airflow-dependent mobilization of sputum. Salivary contamination can be partially corrected by drying the mucus and taking the dry weight for analysis; however, interventions that stimulate mucus secretion can change the hydration of expectorated secretions, making wet-to-dry weight calculations invalid. The actual volume of secretions expectorated is extremely variable from day to day and even at different times of the day, with greater volumes generally produced in the early morning. Finally, increased volumes of collected secretions could represent increased *production* of mucus rather than increased clearance. Measuring expectorated mucus volume can give a global impression of mucus transport only if airway mucus production is stable during the period of measurement, and cough frequency and power do not change.

Sputum color is nearly meaningless as an outcome measurement. The greenish color of infected sputum is most commonly due to myeloperoxidase released from activated neutrophils, and purulent sputum is strongly associated with bacterial growth during an exacerbation of chronic obstructive pulmonary disease.[48] Change in color does not demonstrate clinical benefit, although it may suggest less inflammation.

Sputum Inflammatory Mediators

Sputum inflammatory mediators such as interleukin-8, myeloperoxidase, DNA, and others are fairly easy to measure accurately if the sputum is appropriately collected and processed.[28,29] It is critically important to note that adding drugs to "thin" or solubilize sputum, such as dithiottreitol, that contain free thiol (sulfhydral) groups will depolymerize mucins, but these will also inactivate the antibodies used in enzyme-linked immunosorbent assay (ELISA) assays, rendering the results of these analyses uninterpretable.[29,49]

Clinical Outcome Measures for Long-Term Studies

The outcome measures or end points chosen for short-term interventions can generally be adapted for long-term studies as well. Although there are very few well controlled, adequately powered, and randomized trials using these outcome measurements in short-term trials of mucus clearance therapy, there are even fewer good long-term studies. Thus, although the additional outcomes proposed below could be adapted for long-term studies of these mucoactive interventions, in general there are no definitive clinical trials that clearly support this use.

Decline in Pulmonary Function

It can be hypothesized that improved mucus clearance may affect the rate of decline in pulmonary function over time by reducing the number of pulmonary infections and exacerbations. This is supported by epidemiologic data from the Copenhagen City Heart Study.[50] In that study it was found that chronic mucus hypersecretion was associated with a faster decline in PFT results, with more frequent hospitalization, and with increased death due to pulmonary infection. In order to evaluate the rate of change in pulmonary function over time, clinical trials with long observation times and large numbers of patients are needed. In a small number of studies that have compared different forms of chest physiotherapy, the rate of decline in pulmonary function has been used as an outcome variable.[51–55] Differences between the treatments were found, but different studies identified different clearance techniques as being more effective. At this time, no specific form of chest physiotherapy can be considered as superior to others.[55]

Exercise Capacity

Exercise capacity is related to adequate ventilation, gas exchange, blood circulation, oxygen transport, muscle mass, patient effort, and patient training. Airway mucus retention can affect ventilation and gas exchange and can lead to gas trapping, with an increased RV/TLC, and this can decrease the efficiency of the diaphragm.[39] Tests to measure functional exercise capacity include both laboratory tests, such as treadmill or bicycle ergometry, and field tests, such as the 6-min or 12-min walk test,[56] the shuttle run or walk test,[57] and the step test.[58] The 6-min walk test is most frequently used to evaluate functional exercise capacity. The minimal clinically relevant difference in 6-min walk distance is probably greater than 50 m.[59] Changes in exercise capacity are probably a more sensitive indicator of mucus clearance than usual PFT measurements.

Dyspnea

Dyspnea is a common symptom in patients with pulmonary disease, and more severely compromised pulmonary function.[60] The relationship between dyspnea and airway mucus retention is unclear. When mucus retention has a measurable effect on pulmonary function, a link to dyspnea can be hypothesized. Common measures to quantify dyspnea include the Borg score, Medical Research Council dyspnea score, oxygen cost diagram, and baseline dyspnea index.[61]

Quality-of-Life Scores

Hypersecretion, reduced mucus transport, and airflow obstruction are impairments, whereas chronic coughing, sputum expectoration, and dyspnea can limit the patient in daily activities and can therefore be classified as disability. Chronic coughing, expectoration, and dyspnea can also limit a patient's social functioning and lead to a handicap. Thus, the effects of mucoactive drugs or mucus clearance techniques can also be evaluated as these relate to disability or handicap. An intervention might decrease the impairment severity by improving bronchial mucus transport but could paradoxically have negative effects on disability or handicap, due to dependence on another person or a complicated device, or by the need to regularly take medication. This in turn might limit adherence to therapy. There are few data concerning the psychological and social aspects of mucoactive therapy and mucus clearance techniques and their effect on QOL.[27]

QOL Scores: Generic Questionnaires. These questionnaires can be used either in the general population or in patients with disease. An advantage to these questionnaires is that comparisons can be made between patients and healthy subjects. However, the questions in these questionnaires do not address the specific problems of patients, and the sensitivity for change due to mucoactive therapy is thus low. Examples of generic questionnaires are the Short Form (SF)-36[62] and the Nottingham Health Profile.[63]

QOL Scores: Disease-Specific Questionnaires. Disease-specific questionnaires have been developed to evaluate health-related QOL. In contrast to generic questionnaires, comparison between groups of patients and healthy subjects is usually not possible. Examples of disease-specific health-related QOL questionnaires are the St George's Respiratory Questionnaire, the Chronic Respiratory Disease Questionnaire, the Breathing Problems Questionnaire, and the Cystic Fibrosis Questionnaire (CFQ).

The St George's Respiratory Questionnaire has been validated in many countries and in different languages.[64] It contains questions across 4 dimensions: symptoms, activity, impact, and a total score. Some of the questions in the symptom dimension are related to mucus expectoration. However, only the presence or absence of a symptom is scored. The Chronic Respiratory Disease Questionnaire was developed for patients with chronic airflow limitation, and contains 20 items, which are categorized into 4 dimensions: dyspnea, fatigue, emotion, and mastery.[65] The Breathing Problem Questionnaire was developed by Hyland et al[66] and covers 13 domains. None of these questionnaires have been validated for the specific use of measuring the efficacy of mucoactive therapy.

The Cystic Fibrosis Questionnaire is a disease-specific instrument that measures health-related QOL for persons with CF. Originally developed in French,[67] versions of the CFQ have now been validated in English and other languages.[68] Strong associations have been found between the CFQ and similar scales on the SF-36, although, like the SF-36, this health-related QOL instrument does not specifically test for symptoms associated with sputum production or mucus clearance.

QOL Scores: Symptom-Specific Questionnaires. QOL questionnaires can also be developed specifically for a major symptom or symptom complex. One disease-specific questionnaire developed for problems related to mucus is the "Petty score"[69] that is designed to evaluate the clinical impact of mucoactive therapy in patients with chronic bronchitis. We have evaluated this tool in patients with CF or chronic bronchitis and found that, while there appear to be correlations with sputum physical properties and clearability, it is insensitive for detecting changes in clinical status related to mucoactive therapy.[30]

Days in Hospital, Days of Additional Therapy

Improved airway hygiene may reduce the retention of infected secretions and thus the frequency of respiratory tract infections. As a consequence it might be expected that the frequency of respiratory tract infections is related to days in the hospital. Reisman and colleagues compared a version of the forced expiratory technique to conventional chest physiotherapy in a cohort of patients with CF, and no differences were found in the frequency of hospitalization.[53] Although in 2 studies that assessed the effect of PEP breathing there were fewer exacerbations,[51,54] in another study of PEP[52] this could not be confirmed.

Summary

Mucus secretion and clearance is a complex physiologic interaction that is modified by disease, medical therapy, and a variety of nonmedical and cultural factors. We generally cannot determine in advance which patients are likely to benefit from mucoactive therapy, and the effectiveness of therapy in an individual patient can be difficult to assess. Clinical trials to assess the efficacy of mucoactive therapy must take into account this complexity, and assessment outcomes will differ depending upon the therapy being evaluated, the stage of evaluation (phases of drug or device development), the patient population being studied, and the comparison or control group being compared.

For clinical trials the key end points must be to determine if the intervention is safe, effective, and well tolerated. The choice of safety and efficacy measures as well as the population to be studied will be largely driven by the mechanism of action for the intervention and how that would affect disease process. For example, a medication that reduces the production of *mucus* (not *sputum*) would theoretically be beneficial in severe asthma, where patients "drown" in their mucus,[70] but would be of little or no benefit in CF, where there is decreased mucin in the airway relative to normal mucus or chronic bronchitis sputum.[71]

Safety measurements to be assessed should include diffusion capacity, spirometry, and oxygen saturation. One of the better clinical outcomes of effectiveness is improved functional exercise capacity. Improved airway secretion clearance should decrease airway obstruction, as measured by radioaerosol deposition or as the volume of trapped gas in the chest, assessed via the RV/TLC ratio.

Lack of intervention effectiveness could be due to true lack of benefit, but it is important to remember that adherence to therapy is very poor, especially with the use of airway clearance devices.[22] To get an accurate determination of true effectiveness, adherence must be determined and monitored, especially in trials of longer duration.

Although at this time, radiographic imaging of the lungs is insensitive to changes in secretion clearance, newer techniques that yield higher resolution with less ionizing radiation hold great promise. It would be extremely valuable to have a technique that could quickly, accurately, and safely measure the total burden of airway secretions.

Although QOL can be assessed with a number of well accepted tools, none of these instruments has been validated as an accurate means to determine the effectiveness of mucus clearance therapy,[27] although I am aware of studies underway that should help answer this question. Similarly, although classic PFT equipment is widely available and well standardized, spirometry is inadequate for evaluating the effectiveness of mucus clearance therapy.

Investigators must remember that just because something can be measured, this does not mean that it is a good idea to do so. Adding a large number of outcome measures will increase the complexity of a study as well as the resources needed to conduct the study, the time that each subject must invest in being tested, and it will increase the risk of a falsely positive result occurring by chance alone. A recent study looked at the interrelationship of outcome measures in a clinical trial that compared hypertonic saline to dornase alfa for airway clearance in children with CF. The investigators found that all PFT changes correlated with each other and added no additional value to the analysis of results, but PFT changes did not correlate with changes in exercise tolerance, occurrence of exacerbations, or QOL.[19]

A global assessment of the Cochrane database summaries that looked at published data on airway clearance and physical training effectiveness in CF was published in 2006. Those authors concluded that there were too few long-term data to make definitive recommendations about any of these interventions. They concluded by stating that, "A consensus urgently needs to be reached on which outcome measures are appropriate for physical therapy trials."[54] This RESPIRATORY CARE Journal Conference comes at an opportune time for charting the course that we must follow forward to reach that consensus.

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Discussion

Hess: So what should a therapist do, and what should they measure at the bedside to determine whether some intervention to improve airway clearance is making a difference?

Rubin: It depends on the patient that is being cared for at the bedside. If it is a patient who is ambulatory, whom you can talk to, that is, a nonintubated patient, you can ask them. That's what most of us do, because they're likely to do it if they feel OK, if they think it makes a difference, if their perception is that they can feel better, they can breathe better. Frankly, that's what people are going to do anyway. Measuring whether therapy was productive of sputum or not is unlikely to help. Measuring vital capacity at the bedside is of limited value. Getting them up and doing a shuttle walk—there is a very nice study by Jeff Regnis[1] that showed that exercise capacity was associated with gas trapping. And so it may be that tests like exercise tolerance, shuttle walking, looking at gas trapping (if you want something to measure) may tell you if you're clearing the airways better. As I mentioned yesterday, what we would *really* need for these studies is a whambang way to quantify, perhaps radiographically, the total secretion burden in the airway. Once we have that, we have a license to *really* study these things well. But at the bedside, nothing beats asking the patient.

1. Regnis JA, Alison JA, Henke KG, Donnelly PM, Bye PT. Changes in end-expiratory lung volume during exercise in cystic fibrosis relate to severity of lung disease. Am Rev Respir Dis 1991;144(3 Pt 1):507–512.

Hess: So the traditional, "How much did you bring up and what does it look like?" is not very helpful.

Rubin: No, just as pediatricians are often interested in the contents of diapers (or nappies for those of you from overseas) and that doesn't often help anything, other than to focus on bodily secretions, precious bodily fluids.

MacIntyre: Bruce, that was terrific, as always. Just a comment. You didn't address Dean's question, bring up the idea of exercise testing and functional testing and 6-minute-walk testing, which those of us in the COPD [chronic obstructive pulmonary disease] world are finding increasing useful as a meaningful clinical outcome that can be done fairly quickly, fairly straightforwardly, and perhaps over short periods of time.

Rubin: There are very few data, but those data that have been published[1] tend to suggest that functional exercise capacity—and now they're suggesting shuttle walking as being more reproducible—may be one of the better ways of determining functional outcomes, and this, in turn, is related to mucus properties and mucus clearance. The problem is it has to be done the same way at each institution, and there always appears to be a bit of a training element to it. So you need a well-controlled group, because even the control group is going to have improvements as you become used to it. But, yeah, I think you are absolutely right there.

1. Piquette CA, Clarkson L, Okamoto K, Kim JS, Rubin BK. Respiratory-related quality of life: relation to pulmonary function, functional exercise capacity, and sputum biophysical properties. J Aerosol Med 2000; 13(3):263–272.

MacIntyre: I would point out that the American Thoracic Society has put out a series of standards[1] as to how to do the 6-minute-walk test (but not the shuttle test, which is similar). And I also want to emphasize a point you made that I think is critically important. It is that surrogate end points are not necessarily linked to meaningful clinical outcomes. I'll even take it astep further and say they actually may go in the wrong direction. That's what scares me about surrogate end points.

Those of you in the ICU know that setting ventilators to push pressures and volumes into sick lungs can make blood gases and lung mechanics look very, very good, but at the end of the day actually damage healthier regions of the lungs and kill the patient. So

even though the numbers *look* better, temporally, the outcomes may be in reverse in this particular field. We've said this before at this conference, but making more sputum, as you suggested, actually may be a sign, perhaps, of damage or harm to the airways, and in fact may be going in the *wrong* direction from what might be a meaningful outcome.

1. Enright PL. The six-minute-walk test. Respir Care 2003;48(8):783–785.

Rubin: I would just comment that the CF literature is absolutely *littered* with great ideas that were shown to hurt patients when clinically studied; from mist tents, to IPPB [intermittent positive-pressure breathing], to low-fat diets, to the early gene therapy trials.

MacIntyre: I bet all of them had meaningful surrogate outcomes that looked good initially, before more meaningful clinical outcomes came along and said that they were wrong.

Schechter: That was a nice survey from the micro- to the macro-system perspectives, Bruce. I would like to reinforce and amplify Neil's comment about the relationship between surrogate and clinical outcomes. I think that a great lead-in to this discussion was Duncan's [Rogers] comment yesterday regarding how certain characteristics of pulmonary mucus that lead to better cough clearance lead to worse mucociliary clearance. The reason that surrogate measures are not always predictive of clinical outcomes is that they represent a single aspect of a complex system. Whether we are discussing the human body, the political world, or other complex systems, the challenge is to figure out how a variety of individual components will interact to give you the final outcome of interest. In the end, we can't predict what will work and what won't work until we do tests of the final result. There are lots of interventions that affect a specific component of the system, and it might make perfect sense that these interventions would lead to better clinical outcomes, but then it turns out that they don't, either because we didn't accurately predict the interaction of several known effects (eg, cough clearance and mucociliary clearance), or because a completely new factor that we hadn't considered came into play. So we need to be very careful when extrapolating from surrogate measures to the expectation of an effect on clinical outcomes.

On the other hand, it is extremely difficult and complicated to put together a good clinical trial that's got valid and reliable outcomes. Clinical trials are incredibly clumsy tools that tend to lump together patients who are often quite heterogeneous regarding nuances of clinical characteristics and concurrent therapies. If a drug or other intervention is effective in one type of situation (or patient subgroup) but not in others, and that specific situation or subgroup was not considered when the study was designed, the study might either fail to show effectiveness where it existed or generalize a finding of effectiveness to situations where it does not exist.

This then gets into the question of what do you do at the bedside. Every individual patient is an anecdote—a therapy might or might not be effective in an individual patient, regardless of what clinical trials show. We don't deal with anecdotes when we're talking about clinical research or clinical evidence or whatever, but when you're talking about the individual patient, you're really in a very different world. At best, the results of clinical trials give you an idea of the statistical likelihood that a specific intervention will work for a specific patient.

I just want to make one more comment regarding the problem of studying the effect of interventions on clinical outcomes. There is an important distinction, especially for chronic therapies, between efficacy and effectiveness. A drug's "efficacy" is a measure of how well it works if taken exactly as it should be. A drug's effectiveness is a measure of how well it works when you prescribe it to a patient. We test efficacy in our typical clinical trials, where case definitions, adherence, et cetera are rigorously monitored, but that doesn't necessarily tell you how an intervention will work once it's introduced to clinical practice. And so *effectiveness* studies may contradict efficacy studies because of issues related to proper medication use and adherence, and this is ultimately what we are interested in.

Rogers: These studies are clearly going to be very difficult to perform. Suppose you have drug X, which is a compound you think will alleviate mucus problems in a set of patients in whom mucus in the airway appears to be a clinical issue. Essentially, in the Venn diagram of the 3 components of COPD,[1] you're targeting the patients who have got chronic bronchitis as a predominant component. On that basis, how best to test drug X in those identified patients? Presumably, end point options include feeling better, production of less mucus (because chronic sputum production is something they find annoying, embarrassing, and debilitating), improvement in lung function, and improved exercise capacity. Implementing these clinical variables presents a considerable challenge to effective testing of drug X.

1. Rogers DF. Mucoactive agents for airway mucus hypersecretory diseases. Respir Care 2007;52(9):1176–1197.

Rubin: That is a key question. I would actually answer that question with an answer that we are not even discussing today, because this is a RESPIRATORY CARE Journal Conference. Now I would start off with patients with chronic nasal hypersecretion: inflammation in the lung and lower respiratory tract are often associated; the nose is easier to access in terms of being able to identify secretions, identify inflammation. It's easier to measure nasal patency with anything from

observation to acoustic rhinometry. You are also better able to evaluate whether topical application or systemic application can make a difference.

So if I'm going to be testing effectiveness for something that *may* potentially work in the lower respiratory tract, and it is a general, broadly mucoactive substance, I might be interested in beginning in the nose. Your question, though, dealt with lung therapy in the patients with a chronic bronchitis, and there you need to think about things such as functional exercise capacity, frequency or severity of exacerbations, gas trapping if you're mobilizing secretions that should be reduced. And if you think that this has a specific effect on mucus, you probably want to go on and look at what they cough up to see if it actually *changes* the mucus—reduces the mucins, reduces the amount, whether the benefit you are seeing is actually due to what you *think* you're supposed to be doing. Because that would be good confirmatory evidence if you find a group of subjects, a subgroup that appeared not to get benefit, and you find out that the putative action isn't manifested in their expiratory secretions. You can either suggest that there is something different about their response to therapy, or you can identify those who are nonadherent with therapy.

So I would be careful in doing those initial studies, to try to identify relative outcomes, but at the same time have a double check for adherence, have a double check for whether it's doing what you think it's ordered to do.

Tecklin:[*] That was a wonderful presentation. One thing that you alluded to briefly is something that I think many, if not most, of the airway clearance studies in CF have largely ignored, and that is proper patient selection. We look at some of these airway clearance studies where the authors list the patients and their demographics, and we see patients with pulmonary function values in the 30s included with others who have pulmonary function values in their 80s, 90s, and 100s. I don't need to tell this group that those widely varied values represent CF severities of differing severities. That design flaw in the studies regarding widely differing severities really flies in the face of good research, and I think many of us have been guilty of that in our earlier work.

Rubin: The internist will tell you that chronic COPD is even harder. Are they still smoking or not? How many or them have diabetes, heart disease, take 20 different medications, and do they take them at all? Monitoring adherence is a very interesting, very difficult thing to do, even with things that will measure if a device is being turned on, because turning a device on doesn't necessarily mean that the patient is using it correctly or even using it at all. Adherence is when you do what you're supposed to be doing because it's the right thing. Your mom tells you to clean your room and insists that you do it or you're gonna be punished, and you do it—that's "compliance." If you clean your room because you know you're supposed to clean it, that's "adherence." But there's a third thing that Mark Everard talks about, that if you don't want your mom to hassle you, you kick as much under the bed as you can and then you put all of your toys on the bed and cover them with the blanket, and you tell your mom the room is clean. That is "contrivance." And so, even when you have something like a Vest that can measure how long it's turned on, they can turn it on, leave the room, go do their own thing, and then come back and turn it off. It also can't tell you if it has been used properly, fitting snugly enough to do anything!

Penn:[†] Could I come back to the question of, particularly, trial design or clinical study programs for new therapies. I suggest our interest is in inhibiting mucus secretion in the first place, and one of the challenges is that most surrogate markers, or correlates, get validated through the use of interventions that are effective, and when you start with something that has a completely new mechanism of action, the existing markers and many of the things that you've listed, even if they're scientifically very sound, still wouldn't be accepted in a regulatory world as effectively validated.

I was particularly alarmed or frightened by your statement that the volume of sputum is meaningless, when what we are looking to do is find a way of reducing its production in the first place. So you made a comment that it would be nice to see a way of measuring the total sputum load or mucus load in the airway, and that would get around the problem of the variability in expectorated volume, that may be affected by other factors changing sputum composition. This could, for example, result in more being expectorated, leading to a false negative result. Would you like to expand on that, or does anybody else have anything to comment? Because one of the things we're going to be looking at as we develop a new program is what sort of surrogate markers can we develop or validate alongside the development program.

Rubin: I think that you can better do it, again, in the nasopharynx, in terms of identification, in terms of the lung Duncan [Rogers] and Cees [van der Schans] mentioned yesterday, MRI [magnetic resonance imaging], which can actually distinguish mucus from

* Jan S Tecklin PT MSc, Department of Physical Therapy, Arcadia University, Glenside, Pennsylvania, representing Electromed, New Prague, Minnesota.

† Charles Penn PhD, Syntaxin, Salisbury, Wiltshire, United Kingdom.

tissue density. And using a very high (I think I'm using a 7T coil) magnetic coil, you can scan animals very, very finely and get a *relative* idea, but I don't know that there is *anything* close to that in humans.

Penn: In humans, how similar is the production of mucus in the nasopharynx—at a cellular level and gland level—compared to bronchotracheal region?

Rubin: Fairly similar. And I'm not trying to sell this group on nasal studies. I've personally wrestled with how to design these trials for a very long time. There are even fewer studies that are well conducted relative to nasal clearance, nasal secretions, and things like that. They're just *really* poorly done studies, but I think the possibility is there. I think the accessibility, the acceptability, and the *size* of the airway that you're dealing with may make it a very valuable place to begin studies. And in fact, if you are looking at things like ion transfer and the like in CF, often it was the nose where they began looking at the effects of gene transfer therapy.

Howard:* If the group is interested, I would be willing to relate some of our experience with the FDA [Food and Drug Administration] in evaluating a new mucus-altering agent. We went to the FDA with the compound and presented some of the kind of ideas and questions that have been mentioned here: how do you measure the effect of a drug that's supposed to be altering the amount of mucus that you're producing and has other properties as well? They, in essence, said, "Well, you guys are in a 'white space,' meaning nobody knows how to do this."

They made it clear that our assignment was going to really be 2 parts. One part had to do with showing some change—like, we were extremely interested in cough, for example, related to chronic bronchitis. We could have also talked about measuring volumes of sputum, but what they said was, "You're going to have to do 2 things. One, you're going to have to show that you produced some measurable change, whether it's in cough, or sputum volume, or something like that. But that's not going to be satisfactory for an approval. Second thing you're going to have to do is show that you have improved the *quality of life* of the person." That's a *lot* more difficult assignment.

What we ended up doing was a 3-armed double-blind placebo-controlled trial, at 2 doses of the active drug and a placebo, so it was a pretty large study. Three months of treatment and one month of follow up. We deployed quite an array of measurements. Now, I'm not going to get into the results of the study today, because that's not public yet, but what we did, in terms of the general study, is well known.

But we used quality-of-life tools such as the Saint George's Respiratory Questionnaire, and cough and sputum visual analog scales. We did 6-minute-walk test; we did the classic spirometry; we had the subjects come in monthly for a physical examination and medication adherence assessments.

And, last but not least, we tried to move the technological needle a great leap forward in this study as well, because what we employed in about 20% of the subjects was a fully automated device that uses a real tight-fitting vest that measures things like respiration rate and tidal volume and the amount of activity that the person engages in. It also included a throat microphone, along with some other devices to try to measure cough frequency. The object here was this subset of patients wore this device once a month for a day, so we had 24 hours of continuous data collection with that device.

Just to give you a dollar figure, this trial cost about 6 million dollars, so you're not talking about a small expenditure here, and it took about a calendar year to complete. Importantly, the FDA considered this a Phase 2B trial, meaning we still have to do a pivotal Phase 3 trial to finally get the drug to market in the United States. My point is that the necessary assessments for drug approval are daunting and very expensive.

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* William W Howard PhD, Adams Respiratory Therapeutics, Chester, New Jersey.