Is Extended-Release Guaifenesin No Better Than a Placebo?

In this issue of RESPIRATORY CARE, Hoffer-Schaefer et al[1] report the results of a double-blind randomized placebo-controlled trial examining the effects of guaifenesin on both the volume and physical properties of sputum in patients with acute respiratory tract infections (RTIs). Guaifenesin has been marketed as an FDA-approved over-the-counter (OTC) expectorant medication with annual sales of approximately $135 million in the United States. There is currently a paucity of data suggesting that guaifenesin is an effective expectorant, mucolytic, or cough suppressant. Hoffer-Schaefer et al[1] report the effects of two 600-mg extended-release guaifenesin tablets taken twice daily on sputum volume and sputum properties in adolescents and adults with acute RTIs.

In its natural healthy state, the lung produces mucus on a continuous basis to clear airways, to entrap bacteria and viruses, and to maintain airway hydration. Sputum refers to the expectorated sample of retained mucus in combination with bacteria and inflammatory cells from within the lung and is a manifestation of underlying lung inflammation and infection. There is an increasing understanding of the complexity of the physics of mucus production, transport, and clearance from within the bronchial tree.[2] This clearance of mucus from the lung is dependent on a number of factors, including the rheological properties of the mucus, airway wall factors, and the physical interactions between the mucus and the airway wall.

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Elasticity and viscosity are two of the critical properties of sputum rheology. Elasticity is the ability of a material to return to its original shape after deformation; for example, a rubber ball is highly elastic, whereas clay is plastic. Viscosity is a material's resistance to flow. Honey has a high viscosity and is difficult to pour out of a glass, whereas water has a low viscosity and flows more easily. Mucus is an example of a non-Newtonian fluid, meaning that it has both viscous and elastic properties.

Mucus is generally cleared by ciliary motion and is dependent on factors such as the volume and composition of the mucus, adequate periciliary liquid volume, and ciliary beat frequency. This balance can be upset during RTIs, resulting in the overproduction of particular mucins (notably MUC5AC and MUC5B) and other large polymers within the secretions, including deoxyribonucleic acid, filamentous actin, proteoglycans, and biofilms.[3]

Coughing represents a high-stress high-velocity reflex and so has a direct relationship with viscosity but an inverse relationship with elasticity, meaning that it is easier to expectorate large amounts of viscous mucus than small amounts of elastic mucus.[4] This is akin to squirting out honey from an inverted full plastic bottle with a single shake compared with one with a small smear of honey along its wall. On the other hand, mucus clearance is a low-stress high-frequency force applied by cilia to the airway secretions. This force has a direct relationship with the elasticity of the substance being moved and has an indirect relationship with the viscosity of the fluid. Therefore, there are factors favoring mucus clearance from the lung such as a thin mucus layer, high mucus elasticity, and low mucus viscosity,[4] whereas a thick mucus layer, low mucus elasticity, and high mucus viscosity favor clearance through coughing.[4] Following these principles, the ability of a drug to improve airway clearance is partially dependent on whether the secretions are in the main airways, in which case a drug that enhances cough is preferable. If the mucus obstruction is in the more distal airways, a drug that enhances mucus clearance is preferable.[4]

There are over 50 commercialized compounds purported to have beneficial effects on mucus or its secretion.[4] Broadly, these are classified into expectorants (which increase mucin secretion or increase mucus hydration to a volume that is more easily expectorated by coughing; eg, hypertonic saline), mucolytics (which reduce the viscosity of mucus by dissociating the disulfide bonds in mucins through chemical interactions; eg, N-acetylcysteine), mucokinetics (which increase the transportability of mucus by cough; eg, albuterol), and mucoregulators (which reduce mucus hypersecretion; eg, glucocorticosteroids).[4-6] There is increasing pressure by the FDA on drug companies to demonstrate proof of efficacy and safety of such medications.[7]

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In this report, Hoffer-Schaefer et al[1] report the effects of guaifenesin at a standardized OTC dose on subjective symptomatology and sputum rheology in adolescents and adults with a productive cough from an upper RTI (URTI). The trial is registered (ClinicalTrials.gov registration NCT01046136), and the patient-related outcomes pertaining to this study have been reported previously.[8] In the patient-related outcome aspect of this study, extended-release guaifenesin was found to have no effect on all 3 patient-related outcome markers analyzed as measured by the Daily Cough and Phlegm Diary, Spontaneous Symptom Severity Assessment score, and the Wisconsin Upper Respiratory Symptom Survey.[8] Hoffer-Schaefer et al[1] studied 3 physical aspects of sputum, including interfacial tension using a du Noüy ring distraction method, dynamic rheology using a rheometer (AR1500ex, TA Instruments, New Castle, Delaware), and mucus hydration using total sputum weight and percentage hydration. The authors found no difference in any of these 3 sputum properties with guaifenesin compared to a placebo in adolescents and adults with a productive cough secondary to a URTI. A more detailed breakdown of the clinical subtype of URTI relating to the study cohort has been reported previously and highlights that 82% of the expectorated sputum samples were from patients with rhinopharyngitis, whereas only 8.5% of the patients had acute bronchitis.[8] One might speculate there is a difference in the pathogenesis, sputum origin, and rheology of expectorated sputum from rhinopharyngitis and acute bronchitis, perhaps suggesting that particular subgroups of RTIs may be more amenable to different classes of expectorants.[9] That said, this medication is marketed as an OTC medication for the subgroup of patients studied in this report.

In conclusion, guaifenesin has not been shown in this study to work as an expectorant, as it did not increase the volume of sputum cleared, or as a mucolytic, as it did not alter sputum rheology or the interfacial tension of the sputum, in this cohort of patients compared to a placebo. The FDA's progressive requirements in demonstrating proof of efficacy for new OTC medications is to be commended and suggests that, in time, increased effort should be required to demonstrate efficacy of already available OTC medications that entered the market prior to the current proof-of-efficacy requirements.[7,10]

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