Inhaled Mucomyst (N-Acetylcysteine) in the management of ventilator-dependent acute respiratory failure

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A. Study purpose and rationale

Acute respiratory failure is a common reason for admission to the ICU and it is estimated to be present in 32% of patients on ICU admission with a further 24% of patients developing ARF during ICU stay, accounting for a total of about 56% of all ICU admissions for length > 48 h (Vincent, *et al*.). The poor prognosis of patients with severe but potentially reversible acute respiratory failure has long been recognized. Acute respiratory failure can be due to a number of etiologies such as COPD exacerbation, congestive heart failure, ARDS and pneumonia. In particular, ICU mortality for patients intubated for respiratory failure due to severe pneumonia or pneumonitis (a much different entity than the community-acquired pneumonias treated on an outpatient basis or even those treated on the floors) is estimated to be about 26-54%, with many estimating it to be around 40% (Vincent, *et al*.; Vasilyev, *et al*.). The morbidity and mortality surrounding such patients with pneumonia and acute respiratory failure is likely due to a number of factors surrounding the severity of illness of the patient including failure of other organ systems, as well as the tendencies to develop complications of mechanical ventilation itself such as ventilator-associated pneumonia. Suitably, it has been observed that the probability of survival of mechanical ventilation decreases over time (Esteban, *et al*.).

With this in mind, there have been many methods, often used in combination, to treat a patient in respiratory failure with the intention to successfully wean off the ventilator in a timely fashion. These include treatment of the original cause of respiratory failure itself, i.e. treating the pneumonia with antibiotics, as well as different ways to help with pulmonary toileting such as suctioning, chest physical therapy, and various nebulizers. Mucomyst (N-acetylcysteine)—a relatively inexpensive drug available in intravenous, oral and inhaled formulations—has been studied for its numerous beneficial actions. It reduces disulfide bonds in mucoproteins found in mucus. It is a delivery form of L-cysteine, which serves as a major precursor to the antioxidant glutathione. It reduces the formation of proinflammatory cytokines, such as IL-9 and TNF-α. It also has vasodilator properties by increasing cyclic GMP levels and by contributing to the regeneration of endothelial-derived relaxing factor (Walsh, *et al*.). Due to these antioxidant and mucolytic properties, mucomyst has been studied in the treatment of various disease states, including those pulmonary in nature, such as cystic fibrosis, chronic bronchitis, most recently idiopathic pulmonary fibrosis, as well as numerous critically ill states (Boman G, *et al*.; Gallon AM; Konrad F, *et al*.; Rao, S, *et al*.; Suter PM, *et al*.). It has become clear that N-acetylcysteine has diverse biological actions some of which are of potential therapeutic benefit in the critically ill, but despite research, the role of the drug is unclear in the intensive care setting. A very well tolerated drug, mucomyst has often been used in its nebulized form as part of the pulmonary toileting regimen in ventilated patients. However, there has yet to be a study that demonstrates a benefit in its use in the management of ventilator-dependent acute respiratory failure. It is the purpose of this investigation to study the benefits of nebulized mucomyst (via its mucolytic properties and/or antioxidant properties) in the treatment of respiratory failure. The hypothesis is that with nebulized mucomyst as an adjunct to standard pulmonary toileting and treatment of the etiology of acute respiratory failure, patients have higher rates of recovery from acute respiratory failure.

B. Study Design and Statistical Analysis

This study will be a double-blinded randomized control trial of nebulized N-acetylcysteine compared with placebo (nebulized saline). Consecutive patients admitted to the medical intensive care

unit in acute respiratory failure requiring mechanical ventilation with evidence of pulmonary infiltrate on chest x-ray and either fever and/or elevated white count without the below described exclusion criteria, will be randomized to receive every 6 hours either 3 cc of a 10% solution N-acetylcysteine (mucomyst) via nebulizer or 3 cc of nebulized saline, in addition to treatment of primary ailments and standard pulmonary toileting methods: chest PT, suctioning, and nebulized bronchodilator therapy. The study will be double-blinded, as the patient will be sedated and intubated and unaware of the treatment he is receiving, and the physicians and nurses will not be aware of which each patient is receiving. Nebulized solution will be delivered from pharmacy in comparable containers. However, the solution will be poured into the nebulizer/endotracheal tube apparatus by a third person (unbiased, otherwise not involved in medical care), so as to avoid awareness of the odor of the test drug. Subjects will be monitored for allergic response to the study drug and if there is evidence of an anaphylactic reaction (rash, pruritus, flushing, nausea, vomiting, angioedema, tachycardia, bronchospasm, hypotension, hypertension and/or ECG change), administration of the study drug will be stopped. Blood labs and radiological studies will be monitored per the protocol in the intensive care unit, which includes AST, ALT, bilirubin, PT, serum creatinine, BUN, serum glucose and electrolytes. Endpoint to be studied is proportion of subjects who are successfully extubated by 2 weeks after intubation (the point where most would consider tracheostomy for chronic ventilator dependence). To be considered successfully extubated, the patients must not be reintubated within 24 hours, signifying premature extubation. All patients who died prior to 2 weeks and those still intubated/ventilator-dependent at 2 weeks would be considered treatment failure. Analysis of the data will be performed on an intention-to-treat basis, including all patients that are randomized. Proportion of successfully extubated patients in each group will be compared using chi-square test.

Six hundred patients will be enrolled in each arm. This number is derived from the chi-square test estimating the success of extubation after acute respiratory failure in such a group to improve from 50% to 60%. However, the number also takes into account that approximately 30% of patients admitted to an ICU intubated for acute respiratory failure may not in actuality require significant ventilatory support and are able to be weaned off within 24-36 hours. The benefit of our study drug is hypothesized to be minimal in this group. Thus, to design a study with a power of 80% and an alpha value of 0.05, would require ~400 subjects per arm. The increase to 600 subjects per group is to account for these 30% who would likely get randomized without clear benefit. A study this size will require the involvement of the intensive care units of multiple medical centers with a goal to recruit enough patients within one year.

C. Study Procedure

None

D. Study Drug

N-acetylcysteine (mucomyst) 10% solution via nebulizer is the drug of study. Three milliliters via nebulizer will be administered into the endotracheal tube every 6 hours until extubation and or the study duration, which is 2 weeks. The study drug is a generally well tolerated. However, there are some described adverse reactions to inhaled mucomyst including bronchospasm, rhinorrhea, hemoptysis, nausea, vomiting, drowsiness, fever and chills. There is also a known hypersensitivity/anaphylactic reaction described mostly with intravenous mucomyst. When given as a nebulized treatment, it is known to have a distinct odor and stickiness, hence the need for a 3rd party to administer the drug.

E. Medical Devices

None

F. Study Questionnaires

None

G. Study Subjects

Inclusion criteria: To be included in the study, patients must be 18 years or older, be admitted to the medical intensive care unit in respiratory failure requiring intubation just prior to admission or within 24 hours of admission. Admission chest x-ray must have infiltrates c/w alveolar infiltrates and one or both of leukocytosis (defined as WBC>12) and fever (defined as T>101)—both indicators of infection. The patients will be randomized to receive either mucomyst or placebo.

***Exclusion criteria*:** Patients will be excluded from the study if there is a known hypersensitivity to acetylcysteine, or if the patient has known terminal illness such as metastatic cancer with limited life expectancy.

H. Recruitment of subjects

All patients admitted to the MICU who meet above inclusion criteria without the above exclusion criteria will be considered for inclusion in the study. Unfortunately, most study subjects for this investigation will be unable to give consent requiring sedation while mechanically ventilated. However, for those that can, risks, benefits as well as details of the study will be explained in detail and informed consent will be obtained for participation in the study. In the event that the patient cannot himself consent, consent will be obtained from an authorized representative. In addition, the primary care physician will be notified of the protocol.

I. Confidentiality of study data

Study data will be coded (personal identifiers removed) and stored in a secure location, in accordance with IRB regulations.

J. Potential Conflict of Interest

None

K. Location of the Study

Multicenter study at the medical intensive care units of 5 medical centers with hub at CUMC. Collection to take place over one year

L. Potential Risks

Few if any as outlined in the description of risks of study drug.

M. Potential Benefits

Potential benefit to study subject and generalized population of the use of study drug.

N. Alternative Therapies

None. Other standard of care for management of mechanically ventilated patients will be administered to all patients enrolled in the study.

O. Compensation to Subjects

There will be no compensation to subjects.

P. Costs to Subjects

There will be no cost to subjects.

Q. Minors as Research Subjects

There will be no minors enrolled in this study.

R. Radiation or Radioactive Substances

None

S. References

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