

1

TREATMENT FOR AIRWAY CAST OBSTRUCTION

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a national stage application under 35 U.S.C. 371 of PCT Application No. PCT/US2013/073372 having an international filing date of Dec. 5, 2013, which designated the United States, which PCT application claimed the benefit of priority under 35 U.S.C. 119(e) from U.S. Provisional Application No. 61/733,798 filed Dec. 5, 2012, both of which are incorporated herein by reference in their entirety.

GOVERNMENT SUPPORT

This invention was made with Government support under grant number U54 ES015678 awarded by the National Institutes of Health (NIH). The Government has certain rights in this invention.

FIELD OF THE INVENTION

The field of the present invention is methods for treatment of airway obstruction due to fibrin-containing cast formation.

BACKGROUND OF THE INVENTION

Sulfur mustard (bis(2-chloroethyl)sulfide; SM) is a vesicant and chemical weapon used in warfare during much of the 20th century, and which remains in the stockpiles of multiple nations today (Syria, Iran, North Korea, Libya, United States, and possibly others). SM exposure affects the eyes, skin, upper airways and lungs. After a brief latent period, respiratory failure and death can develop within 12-48 hours. Despite a century of study, the mechanisms responsible for SM's toxic effects remain unsolved, and clinically effective rescue therapies or antidotes are not available.

Initial reports of human SM inhalation toxicity in the early 1900s described the presence of airway obstructive necrotic debris/mucosa, or 'pseudomembranes', in the large airways of victims, and these were more recently confirmed in the victims of the Iran-Iraq war (Eisenmenger, W. et al., 1991, *J Forensic Sci* 36:1688-1698; Willems, J. L., 1989, *Ann Med Milit Belg* 3S:1-61). Severe such lesions have been reported lead to respiratory compromise with need for artificial ventilation, and death in 80% of those needing intubation (Willems, J. L., 1989, *Ann Med Milit Belg* 3S:1-61). Further, chronic conducting airway lesions, such as bronchiolitis obliterans, tracheal/bronchial stenosis and chronic bronchitis, are commonly found in SM inhalation survivors months to years after exposure (Willems, J. L., 1989, *Ann Med Milit Belg* 3S:1-61; Ghanei, M. et al., 2008, *Respir Med* 102:825-830), while chronic alveolar or parenchymal injury is less frequent. Therefore, airway injury predominates during both the acute, as well as the chronic phases of SM-induced lung injury.

Airway obstruction from fibrin casts represents one form of a disorder commonly referred to as plastic bronchitis. This is a rare condition characterized by formation of branching bronchial casts that partially or completely obstruct the tracheobronchial tree, often leading to life-threatening respiratory failure. Even though inhalation of chemicals like sulfur mustard can lead to the development of

2

plastic bronchitis, it can also occur due to causes other than chemical inhalation. While occasionally seen in adults (Watanabe, K. et al., 2008, *Intern Med* 47:1549; Eberlein, M. H. et al., 2008, *Am J Med Sci* 335:163-169), plastic bronchitis not due to chemical inhalation is a disorder affecting mostly children. It can develop after Fontan surgery for congenital cyanotic heart diseases (Goo, H. W. et al., 2008, *Pediatr Radiol* 38:989-993; Do, T. B. et al., 2009, *Pediatr Cardiol* 30:352-355; Costello, J. M. et al., *Pediatrics* 109:e67; Heath, L. et al., 2011, *Pediatr Cardiol* 32:1182-1189; Wakeham, M. K. et al., 2005, *Pediatr Crit Care Med* 6:76-78; Brogan, T. V. et al., 2002, *Pediatr Pulmonol* 34:482-487; Seear, M. et al., 1997, *Am J Respir Crit Care Med* 155:364-370), or after various bronchopulmonary diseases such as asthma (Tonan, M. et al., 2011, *J Anesth; Pawar, S. S. et al., 2011, Ann Otol Rhinol Laryngol* 120:697-699), cystic fibrosis (Mateos-Corral, D. et al., 2009, *Pediatr Pulmonol* 44:939-940; Waring, W. W. et al., 1967, *Pediatrics* 39:166-175), acute chest syndrome of sickle cell disease (Moser, C. et al., 2001, *Chest* 120:608-613), viral lower respiratory tract infections including H1N1 (Deng, J. et al., 2010, *Chest* 138:1486-1488), neoplasms such as lymphoma (Kuperman, T. et al., 2006, *Pediatr Pulmonol* 41:893-896), chemical or thermal inhalation injuries (Eberlein, M. H. et al., 2008, *Am J Med Sci* 335:163-169; Pruitt, B. A., Jr., 1974, *Clin Plast Surg* 1:667-691; Cox, R. A. et al., 2003, *Am J Respir Cell Mol Biol* 29:295-302; Veress, L. A. et al., 2010, *Am J Respir Crit Care Med* 182:1352-1361) or idiopathic causes (Krenke, K. et al., 2010, *Respiration* 80:146-147). Presenting symptoms include wheezing, coughing, expectoration of rubbery casts, chest pain, hypoxemia, and/or frank respiratory distress (Brogan, T. V. et al., 2002, *Pediatr Pulmonol* 34:482-487; Madsen, P. et al., 2005, *Paediatr Respir Rev* 6:292-300). Examination of patients with plastic bronchitis, regardless of etiology, reveals wheezing or absent breath sounds over affected regions, while chest radiographs can show segmental lung collapse, or bilateral patchy consolidations often misdiagnosed as pneumonia (Madsen, P. et al., 2005, *Paediatr Respir Rev* 6:292-300). Diagnosis is made either by a history of cast expectoration, or by bronchoscopic or chest CT findings of casts within airways (Eberlein, M. H. et al., 2008, *Am J Med Sci* 335:163-169; Goo, H. W. et al., 2008, *Pediatr Radiol* 38:989-993). Mortality from plastic bronchitis occurs due to respiratory failure related to central airway obstruction, and is more severe in those with underlying cardiac abnormalities (mortality rate of 44-60%) (Brogan, T. V. et al., 2002, *Pediatr Pulmonol* 34:482-487; Madsen, P. et al., 2005, *Paediatr Respir Rev* 6:292-300; Zahorec, M. et al., 2009, *Pediatr Crit Care Med* 10:e34-36).

Treatment of plastic bronchitis, regardless of etiology, has been based primarily on anecdotal evidence reported from individual affected patients. Previously tried medications have included inhaled or systemic corticosteroids (Wang, G. et al., 2006, *Acta Pharmacol Sin* 27:1206-1212), mucolytics (Eberlein, M. H. et al., 2008, *Am J Med Sci* 335:163-169), antibiotics (Shinkai, M. et al., 2005, *Paediatr Respir Rev* 6:227-235), pulmonary vasodilators (Haseyama, K. et al., 2006, *J Thorac Cardiovasc Surg* 132:1232-1233), and anticoagulants such as heparin (Desai, M. H. et al., 1998, *J Burn Care Rehabil* 19:210-212). Non-pharmaceutical treatments have included cast removal via bronchoscopy (Silva, R. C. et al., 2011, *Arch Otolaryngol Head Neck Surg* 137:401-403), vest therapy, fenestration of the Fontan circuit (Wilson, J. et al., 2005, *Pediatr Cardiol* 26:717-719), thoracic duct ligation (Shah, S. S. et al., 2006, *Ann Thorac Surg* 81:2281-2283), AV synchronization (Barber, B. J. et al., 2004, *Pediatr Cardiol* 25:73-76), ECMO (Tonan, M. et al.,