

Aerosol furosemide for dyspnea: Controlled delivery does not improve effectiveness



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ARTICLE INFO

Keywords:

Dyspnea

Furosemide

Palliative care

Symptom management

ABSTRACT

Aerosolized furosemide has been shown to relieve dyspnea; nevertheless, all published studies have shown great variability in response. This dyspnea relief is thought to result from the stimulation of slowly adapting pulmonary stretch receptors simulating larger tidal volume. We hypothesized that better control over aerosol administration would produce more consistent dyspnea relief; we used a clinical ventilator to control inspiratory flow and tidal volume. Twelve healthy volunteers inhaled furosemide (40 mg) or placebo in a double blind, randomized, crossover study. Breathing Discomfort was induced by hypercapnia during constrained ventilation before and after treatment. Both treatments reduced breathing discomfort by 20% full scale. Effectiveness of aerosol furosemide treatment was weakly correlated with larger tidal volume. Response to inhaled furosemide was inversely correlated to furosemide blood level, suggesting that variation among subjects in the fate of deposited drug may determine effectiveness. We conclude that control of aerosol delivery conditions does not improve consistency of treatment effect; we cannot, however, rule out placebo effect.

1. Introduction

Dyspnea that persists despite maximal treatment of the underlying disease (refractory dyspnea) is a common cause of patient suffering (Kamal et al., 2011). At present, systemic opioids are the only evidence-based pharmacologic treatment available to alleviate refractory dyspnea (Bausewein et al., 2008; Currow et al., 2011; Dudgeon and Rosenthal, 1996; Ekstrom et al., 2015; Jennings et al., 2002). Opiates are perceived to have many disadvantages including constipation, confusion, nausea, respiratory depression and regulatory barriers (Currow et al., 2011; Rocker et al., 2012). Inhaled furosemide has shown promise in relieving refractory dyspnea with none of these side effects. A chloride channel blocker commonly used as a diuretic, furosemide also acts on vagal pulmonary receptors when administered as an aerosol (Sudo et al., 2000). Experiments conducted in rats have shown that slowly adapting pulmonary stretch receptors (which respond to inflation) are profoundly sensitized by furosemide while rapidly adapting stretch receptors (which respond to lung collapse) are desensitized. This generates vagal afferent traffic that presumably provides an illusory report of increased tidal volume to the brain.

Increased tidal volume in humans relieves air hunger via vagal mechanoreceptors (Manning et al., 1992); thus it is proposed that aerosol furosemide acts through this pathway to effect relief by mimicking larger tidal volume (Moosavi et al., 2007). Air hunger is the most common form of clinical dyspnea (O'Donnell et al., 2013; Smith et al., 2009) and is associated with severe breathing discomfort; thus, it is reasoned that aerosol furosemide might provide a non-opiate treatment for many cases of refractory dyspnea.

Aerosolized furosemide has been tested as a treatment for dyspnea in controlled laboratory studies and small clinical trials (Jensen et al., 2008; Kohara et al., 2003; Moosavi et al., 2007; Nishino et al., 2000; Ong et al., 2004; Wilcock et al., 2008). Aerosolized furosemide administered at a dose of 20–40 mg has proven effective in many individuals, but it has also been shown not to reduce dyspnea in many others. Large inter-individual variation in the perceptual response to inhaled furosemide is evident in all published studies.

The source of this wide variability in treatment effect is unknown, but several mechanisms can be postulated to explain lack of treatment effect in certain individuals. Inconsistent aerosol drug delivery is one of the most obvious possible mechanisms. Control of inspiratory flow or

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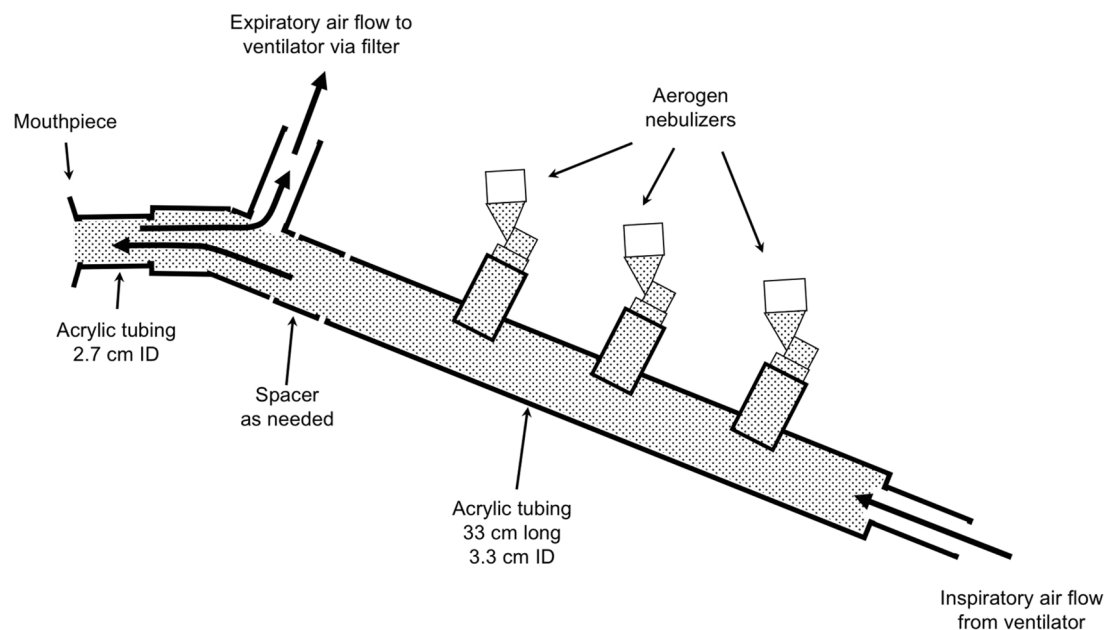


Fig. 1. Aerosol delivery system.

Three nebulizer heads are mounted on a clear acrylic manifold, the inspiratory line of the mechanical ventilator is connected to the right extremity of the manifold, the expiratory line is connected close to the mouthpiece (upward arrow). A spacer tube of similar diameter and 5 cm or 10 cm length can be added between the expiratory line and the nebulizer heads in order to provide a leading aerosol-free space.

inspired volume during aerosol administration is poorly described, if at all, in published studies of furosemide inhalation. Inspiratory flow and tidal volume are key parameters in efficiency and location of particle deposition; if flow is high, particles will impact in the oropharynx and upper airways, not deeper in the lung where the slowly adapting stretch receptors are found (for more detailed description, see review in (Bennett et al., 2002; Brain and Valberg, 1979; Moren et al., 1994)). In addition, most published studies report administering drug via breathe-through nebulizers; aerosol generated during expiration is lost into the room under these conditions, so that the actual inhaled dose would vary depending on the ratio of inspiratory to expiratory time.

The variability of furosemide response could also stem from variable individual sensitivity to the relief of dyspnea by stimulation of slowly adapting pulmonary stretch receptors. The potency of this neural pathway may vary among individuals due to differences in afferent input and central nervous system processing.

We tested the hypothesis that better control over aerosol administration would produce more consistent dyspnea relief. We also tested the hypothesis that furosemide works poorly in those individuals who exhibit an otherwise weak tidal volume relief.

In a crossover study, we used a laboratory model of dyspnea in which graded levels of hypercapnia were delivered to healthy subjects during constrained ventilation. Subjects experienced the same dyspnea challenge before and after treatment with aerosol furosemide and aerosol saline. Inspiratory flow and tidal volume were controlled during aerosol administration. We also compared the subjects' response to inhaled furosemide to the response to two "secondary" treatments designed to provide better understanding of mechanism: 1) We tested the response to larger tidal volumes to assess the potency of the pulmonary stretch receptor relief pathway. 2) We tested the response to intravenous furosemide to address the possibility that aerosol furosemide acts through the systemic effect of absorbed furosemide.

2. Methods

2.1. Subjects

This protocol was approved by the Committee on Clinical

Investigations (Institutional Review Board) at Beth Israel Deaconess Medical Center. All subjects gave written informed consent. They were informed that we were studying shortness of breath, that they would be uncomfortable for periods during the study, and that they could interrupt procedures at any time. They were also informed that, while the drug was approved for use in other contexts, administration via inhalation was investigational (FDA IND 108667). On the first preliminary day subjects completed the Brief Symptom Inventory-18 to assess general psychological distress. Exclusion criteria are shown in Supplement section "Subjects: Selection and Characteristics". Twenty-three subjects signed consent and drug treatment data sets were obtained and analyzed for 12 subjects. Reasons for elimination of subjects from study or the analysis are in Supplement section "Subjects: Selection and Characteristics"(Table S-1). One data set was discarded before further analysis due to later discovery of a disqualifying event, thus data from 11 subjects are presented. Characteristics of the subjects are shown in Supplement section "Subjects: Selection and Characteristics"(Table S-2).

2.2. Aerosol delivery

To better control and optimize aerosol deposition, we used a standard clinical volume-control ventilator to control inspiratory flow and volume (Siemens Servo 900c, Siemens Elema AB, Solna, Sweden). Subjects were ventilated through a mouthpiece. The setup included three Aeroneb Pro-X nebulizers (Aeroneb Solo, Aerogen Ltd, Galway, Ireland) connected to 3 nebulizer heads mounted on a 3.5 cm × 38 cm ID acrylic manifold. Spacer tubes of similar diameter and 5 cm or 10 cm length could be added in order to provide a leading aerosol-free space proportional to the subjects predicted VC (0, 50 or 100 ml as needed to scale the volume to the size of the subject); this was done to minimize delivery of aerosol to the alveoli, which are beyond the slowly adapting stretch receptors that are the presumed target of the drug. This manifold was connected to the inspiratory and expiratory lines of the ventilator and to a mouthpiece of similar internal diameter (Fig. 1). Large diameter tubing and a large mouthpiece were used in the aerosol pathway to minimize gas velocity, thus minimizing particle impaction in oropharynx; the minimum cross sectional area of the external aerosol

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