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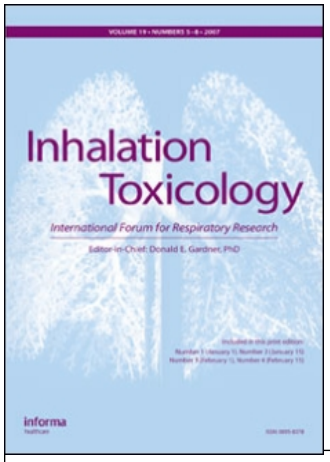

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Dyspnea is the hallmark symptom of some respiratory diseases such as chronic obstructive pulmonary disease and bronchiolitis and is a major reason for which these patients seek medical attention. We performed a randomized triple-blind controlled crossover clinical trial in which we compared the efficacy of inhaled furosemide (4 ml equal to 40 mg in 10 min) with placebo (4 ml of 0.9% saline solution) in 41 mustard gas-exposed patients. Dyspnea index, visual analog scale (VAS), and pulmonary function test results were obtained before and 4 h after treatments. Results showed that both furosemide and placebo significantly decreased VAS and dyspnea index and increased FEV_1, FVC, and FEV_1/FVC, while there was no difference between the two drugs in these effects (*p* values .23, .61, .81, .36, and .27, respectively). Our results failed to address the previously reported effects of inhaled furosemide on dyspnea. In fact, we suggest that patients with a previous exposure to sulfur mustard, in which chronic bronchitis and bronchiolitis are the most suggested underlying mechanisms, may not benefit from furosemide to alleviate their dyspnea.

Sulfur mustard (SM) has been the most widely used chemical warfare agent in the past century. SM is responsible for respiratory injury that may not manifest for many years (Dompeling et al., 2004), such as chronic bronchitis, and bronchiectasis (Ghanei et al., 2004; Emad & Rezaian, 1997), and constrictive bronchiolitis, as reported in recent pathological studies (Ghanei et al., 2004; Aghanouri et al., 2004; Beheshti et al., 2006; Thomason et al., 2003; Ghanei et al., unpublished data).

Dyspnea is the hallmark symptom of some respiratory diseases such as chronic obstructive pulmonary disease (COPD) and bronchiolitis (Ong et al., 2004; Zoorob & Campbell, 2003), and is a major reason for which these patients seek medical attention (Fabri et al., 2004; Ong et al., 2004). Some treatments have been used in the management of dyspnea. Recently, there is some evidence in favor of efficacy of inhaled furosemide in the management of dyspnea. Inhalation of furosemide has been shown to have an inhibitory effect on experimentally induced cough (Ventresca et al., 1990), prevent bronchoconstriction in patients with asthma (Bianco et al., 1988, 1989; Robuschi et al., 1987; Tanigaki et al., 1997), and attenuate the sensation of experimentally induced dyspnea in healthy subjects (Nishino et al., 2000; Bianco et al., 1988) and patients with COPD (Ong et al., 2004).

However, the underlying mechanism of action of inhaled furosemide has not been fully elucidated. Some studies have suggested that furosemide inhibits liquid and mucus secretion from submucosal glands (Solway & Leff, 1991), enhances paracellular water movement (Freed et al., 1996), exerts modulatory effects on inflammatory mediators (Anderson & Wei, 1991; Barnes, 1993), reduces airway temperature variation through local airway vasodilation (Gilbert et al., 1994), dilates bronchial tree (Ono et al., 1997; Rodriguez Vazquez et al., 1998), or dilates bronchial arteries while sparing bronchial airways (Corboz et al., 1997). Some other studies have suggested that inhaled furosemide may indirectly act on vagally mediated sensory nerve endings in airway epithelium, and thereby inhibits the sensation of respiratory discomfort (Chung & Barnes, 1994).

Nonetheless, most of these studies have been performed in normal subjects or COPD and asthmatic patients, and no study has been performed in patients suffering from chronic complications of exposure to SM, in which the underlying pathologic mechanism may be different from the other mentioned diseases; here an irreversible underlying airway disease rather than a reversible airway or irreversible parenchymal disease mechanism exists. Should furosemide exert its modulatory effects on nerve endings, its effects would also be observed in SM-exposed patients. Therefore, we performed a randomized triple-blind controlled crossover clinical trial to evaluate the efficacy of inhaled furosemide in mustard gas-exposed patients.

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METHOD

The patients of this study were those with a history of previous exposure to sulfur mustard and in a convenience sampling method were chosen among those who had been admitted in emergency unit or internal medicine wards of Baqiyatallah or Sasan hospitals—major university hospitals that provide tertiary medical care for patients exposed to chemical warfare agents—with a complaint of dyspnea, from July 2006 till December 2006. All patients had signed an informed consent before participating in the study and all procedures were conducted in accordance with the principles of declaration of Helsinki. The exclusion criteria were (1) a contraindication for furosemide use and (2) an accompanying disease in which other drugs effective for dyspnea were used. For this, all patients had undergone high-resolution computed tomography (HRCT) and spirometry before. In HRCT, significant air trapping (more than 25%), especially on expiratory films, mosaic oligemia and decreased size of vessels, bronchial wall thickening, and bronchiectasis were considered as evidence for bronchiolitis (Müller & Miller, 1995); other diseases such as emphysema and asthma were also excluded by spirometry and HRCT. Before this study, all patients were on a routine treatment of a long acting bronchodilator, an inhaled corticosteroid, *N*-acetylcysteine, and possibly short-term systemic steroids. However, these medications were not stopped during this study. The study was performed in two consecutive days in a triple-blind, randomized, crossover design during which qualified subjects were randomly assigned to either of the two treatment groups (placebo–furosemide or furosemide–placebo). The randomization was performed by a blinded physician using a random number table; the sequence was masked until completion of the statistical analysis. The patients were asked to inhale furosemide (4 ml equal to 40 mg in 10 min; Kimidarou, Tehran, Iran) or placebo (4 ml of 0.9% saline solution), administered by means of a nebulizer. After a 24-h interval without intervention (washout period), the patients were then treated with the other treatment modality of the pair (placebo or furosemide).

During the study, the following data were obtained: Dyspnea was evaluated and quantified using the Modified Medical Research Council (MMRC) dyspnea scale (Brooks, 1982, Table 1) and visual analog scale (VAS), before and 4 h after receiving furosemide or placebo. VAS is a standard method in which each patient is asked to rate the intensity of sensation of dyspnea (Adams et al., 1985). In our study, the analog scale consisted of a vertical straight line, 100 mm in length with 10 equally spaced markers. It was labeled 100 at the top and 0 at the bottom. Patients were instructed to mark a spot on the line indicating the sensation of respiratory discomfort at that point in time. The numerical value of zero indicated "no sensation at all" and 100 indicated a sensation that was "intolerable." This method was also validated and used in some of our previous studies (Ghanei et al., 2007). Dyspnea was defined as an unpleasant urge to breathe with no further clarification or definition given. All patients underwent a pulmonary function test (PFT), measuring forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), peak expiratory flow (PEF), and FEV_1/FVC ratio, before and 4 h after drug administration. Respiratory rate, as an index for respiratory distress, was recorded before, in the fifth minute during, immediately after, and 0.5, 1, 2, and 4 h after treatment.

TABLE 1
Modified Medical Research Council (MMRC) dyspnea index (SEPAR)

0	No dyspnea except for very intense efforts
1	Dyspnea with accelerated walking or when climbing a hill
2	The patient walks more slowly than people his age
3	The patient has to stop after walking for 5 minutes
4	Dyspnea at dressing or undressing; cannot leave home

We analyzed the obtained data (VAS scores, spirometry results, and respiratory rate) after placebo inhalation and after furosemide inhalation using two-tailed paired *t*-tests, or repeated-measure analysis of variance (ANOVA). The difference between placebo and furosemide was analyzed using two-tailed independent $t-$tests. All data were analyzed by SPSS version 13.0; $p < .05$ was considered as statistical significance level.

RESULTS

The baseline demographic and pulmonary function data of the patients are shown in Table 2. At the time of study, all patients (100%) presented dyspnea and cough as their main complaint, while sputum production (60%), hemoptysis (46.7%), and chest pain (40%) were the other frequent complaints in the patients. None of the patients was a smoker. Among the 41 patients who attended and completed the study, 20 received placebo and 21 received furosemide first, randomly. Analysis showed that VAS,

TABLE 2
Baseline anthropometric and pulmonary function data of patients, presented as mean ± SD (range)

Age (yr)	46.3 ± 11.11 (32–83)
Years from exposure	23.1 ± 1.56 (20–25)
Weight (kg)	70.9 ± 10.87 (34–93)
Height (cm)	173.2 ± 5.83 (162–185)
VAS	81.15 ± 20.35 (40.0–100.0)
FEV_1(L)	1.66 ± 0.65 (0.57–3.03)
FEV_1% predicted	44.04 ± 16.61 (16.60–85.0)
FVC (L)	3.02 ± 0.80 (1.14–4.53)
FVC % predicted	64.06 ± 20.64 (25.0–106.0)
FEV_1/FVC	53.68 ± 13.67 (20.0–78.0)
FEV_1/FVC % predicted	66.25 ± 15.83 (26.0–98.0)

TABLE 3
Pulmonary function results before and after placebo or furosemide

Parameter	Before placebo	After placebo	Before furosemide	After furosemide
FEV_1(L)	1.71 ± 0.65	$2.22 \pm 0.65^{**}$	1.71 ± 0.69	$2.23 \pm 0.72^{\dagger\dagger}$
FEV_1 % predicted	45.79 ± 16.40	$59.99 \pm 15.74^{**}$	44.96 ± 17.20	$59.90 \pm 17.46^{\dagger\dagger}$
FVC (L)	3.18 ± 0.78	$3.58 \pm 0.42^{*}$	3.18 ± 0.80	$3.71 \pm 0.64^{\dagger}$
FVC % predicted	66.71 ± 22.04	$77.99 \pm 10.83^{*}$	66.14 ± 22.45	$80.13 \pm 14.39^{\dagger}$
FEV_1/FVC	55.94 ± 11.88	$66.35 \pm 11.20^{**}$	55.94 ± 12.19	$66.14 \pm 17.35^{\dagger}$
FEV_1/FVC % predicted	68.94 ± 11.91	$79.04 \pm 12.78^{**}$	68.87 ± 12.33	$78.11 \pm 12.89^{\dagger}$
PEF rate (L/min)	4.12 ± 2.14	3.49 ± 1.05	4.05 ± 2.17	3.46 ± 1.05
PEF rate % predicted	48.21 ± 23.86	40.73 ± 12.52	47.01 ± 24.41	40.46 ± 14.06
VAS	81.22 ± 20.21	$60.37 \pm 19.95^{**}$	82.93 ± 19.30	$58.05 \pm 22.73^{\dagger\dagger}$
Dyspnea index	3.62 ± 0.59	$2.41 \pm 0.97^{**}$	3.62 ± 0.54	$2.28 \pm 1.07^{\dagger\dagger}$

Note. Values are means $\pm$ SD. Significant differences indicated by $^{*}p < .05$, $^{**}p < .001$ compared with values before placebo; †, $p < .05$, ††, $p < .005$ compared with values before furosemide; ‡, $p < .05$, compared with values before furosemide and after placebo.

dyspnea index, and spirometric measures were not significantly different at the beginning of the first and second days of drug use (p values of .59, .89, .33, .52, .61, and .19 for VAS, dyspnea index, FEV_1, FVC, FEV_1/FVC, and PEF, respectively), indicating that the washout period was effective and on the second day there was no effect of the drugs used in the first day. Also, these measures were not significantly different in patients who had received either furosemide or placebo at the first day (p values of .38, .61, .62, .33,.33, and .58 for VAS, dyspnea index, FEV_1, FVC, FEV_1/FVC, and PEF, respectively) or the second day of trial (p values of .12, .63, .82, .73, .64, and .65 for VAS, dyspnea index, FEV_1, FVC, FEV_1/FVC, and PEF, respectively). Table 3 shows the data of patients before and after inhalation of placebo or furosemide. Both furosemide and placebo significantly decreased VAS and dyspnea index. Furosemide reduced VAS by 24.88 ± 15.68 ($p < .001$) and dyspnea index by 1.32 ± 1.04 ($p < .001$), while placebo decreased VAS and dyspnea index by 20.63 ± 13.60 ($p < .001$) and 1.18 ± 0.90 ($p < .001$), respectively. There was no difference between the two drugs in reducing VAS and dyspnea index (p values .23 and .61, respectively). Administration of furosemide significantly increased predicted percents of FEV_1, FVC, and FEV1/FVC but not PEF (p values $<.001$, .024, .002, and .145, respectively). After using placebo, FEV_1, FVC, and FEV_1/FVC significantly increased (p values .001, .017, and .020, respectively) while a nearly significant decrease in PEF was observed ($p = .055$). The effect of furosemide and placebo on FEV_1, FVC, FEV_1/FVC, and PEF was not significantly different (p values .81, .36, .27, and .84, respectively). Neither furosemide nor placebo exerted any significant effect on respiratory rate (p values .41 and .06, respectively; Figure 1). At the end of the trial, no patient reported any side effects, including an urge to urinate.

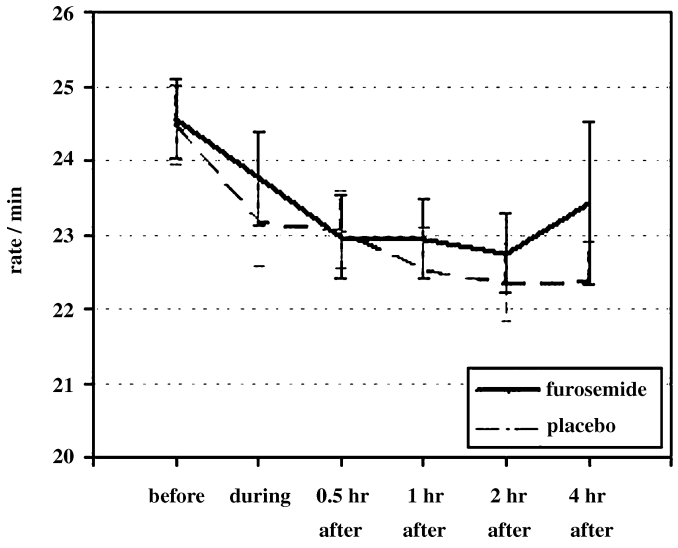

FIG. 1. Respiratory rates of patients before, during, and after treatment with furosemide (solid black line) and placebo (dashed gray line). The bars represent SEM.

DISCUSSION AND CONCLUSIONS

Furosemide is a loop diuretic that acts in the kidney by inhibiting the $Na^+/K^+/2Cl^-$ cotransporter in the ascending limb of the loop of Henle. It was shown that inhaled furosemide could exert modulatory effects on cough and asthma (Ventresca et al., 1990; Bianco et al., 1988, 1989; Robuschi et al., 1987; Tanigaki et al., 1997), which was related to bronchodilation (Ono et al., 1997; Rodriguez Vazquez et al., 1998).

Some studies have tried to postulate mechanisms other than bronchodilation for effects of inhaled furosemide. It has been suggested that inhaled furosemide has a primary effect on the airway epithelium and may influence the responsiveness of sensory nerve endings (Chung & Barnes, 1994); Ong et al. (2004),

in a study on 19 patients with COPD, showed that inhalation of furosemide alleviates the sensation of dyspnea induced by constant-load exercise testing, which was also consistent with the findings of Nishino et al. (2000), who demonstrated that inhaled furosemide greatly alleviates the sensation of dyspnea induced experimentally by breath holding and by a combination of resistive loading and hypercapnia in 12 normal subjects. All these studies have attributed the effects of furosemide to the airway epithelium and responsiveness of sensory nerve endings; however, Knox and Ajao, in an in vitro model, showed that furosemide could not inhibit contraction either in bovine or human trachea, whether they were deepithelialized or had intact epithelium (Knox & Ajao, 1990).

Moreover, acute bronchodilator effect of furosemide is questionable (Cavaliere & Masieri, 2002) and its effectiveness in acute exacerbation of asthma is unproved (Gonzalez-Sanchez et al., 2002; Pendino et al., 1998; Hinckley, 2000). Karpel et al. showed that the combination of furosemide and metaproterenol resulted in a change in FEV1 percentage that was not statistically different compared with metaproterenol alone (Karpel et al., 1994). It has also been shown that furosemide has no direct effect on the airway smooth muscle in vitro.Corboz et al. showed that furosemide dilated bronchial arteries, but not bronchial smooth muscle (Corboz et al., 1997).

Our results showed that furosemide could decrease VAS and dyspnea index and improve FEV_1, FVC, and FEV_1/FVC, which was not significantly different from placebo (normal saline). The placebo effect was also reported by some other studies (Nishino et al., 2000; Noseda et al., 1992, 1997). In one study, nebulized saline was reported by asthmatics to cause an improvement, both clinically and in VAS (Noseda et al., 1992). Other studies have provided arguments in favor of a nonspecific reduction in dyspnea related to the use of either nasal prongs (Liss & Grant, 1988) or a face mask (Schwartzstein et al., 1987). The placebo effect may be due to the nebulized form of use, decreasing respiratory rate or increasing the airways humidity (Noseda et al., 1997). Some suggest that this effect is due to the action of water on the surface film of surfactant, thus decreasing airways resistance (Hasham et al., 1981). However, the exact mechanism needs to be elucidated. One reason for the difference between our results and some previous work is that most of them were performed in asthmatic or COPD patients or normal subjects, while our study was performed on patients with a previous exposure to sulfur mustard. Several studies have shown that these patients suffer from slow-evolving respiratory complications, such as bronchiolitis, asthma and chronic bronchitis, emphysema, bronchiectasis, and lung fibrosis even 20 yr after exposure, which manifests by dyspnea, cough, and sputum as the main chief complaints. Some suggest that all aspects of different disorders addressed before are various presentations of bronchiolitis, which is the original nature of the pathology in these patients (Aghanouri et al., 2004; Thomason et al., 2003; Ghanei & Amini Harandi, 2007). In bronchiolitis, (1) no or little parenchymal injury exists and (2) the pathology centered on the airways is irreversible, rather than reversible in asthma. Furthermore, the patients involved in our study suffered from severe disease. This may make them prone to more severe epithelial and nerve ending injury, making current treatments less efficient. Another reason for the observed difference is that we evaluated the effects 4 h after treatment (quite a bit longer than the periods used in Nishino et al., 2000, and Ong et al., 2004), suggesting that the effects of furosemide on airways and epithelium are not long-lasting and may fade soon in time (Tanigaki et al., 1997). Our results are also in accordance with some previous ones. Furosemide failed to show any effect in acute asthma when added to salbutamol (Pendino et al., 1998), whether in children (Gonzalez-Sanchez et al., 2002) or in adult patients with acute exacerbations of asthma (Hinckley, 2000). Moreover, furosemide failed to show any benefit on airway resistance and functional residual capacity in children with bronchiolitis, either in the symptomatic or in the symptom-free period (Van Bever et al., 1995).

In conclusion, in previous studies inhaled furosemide had shown some controversial effects in the treatment of respiratory diseases such as asthma and COPD; however, our results suggest that patients with a previous exposure to sulfur mustard, in whom the underlying mechanism is suggested to be consistent with chronic bronchitis and bronchiolitis, may not benefit from furosemide to alleviate their dyspnea. Further studies are suggested to investigate this more.

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