Inhaled Furosemide Is Not Effective in Acute Asthma*

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As previous studies have suggested that inhaled furosemide may have a protective effect against certain types of provocative challenges in asthmatic subjects, we investigated the role of furosemide in treating acute asthma exacerbations. Twenty-four patients (n=24) with acute asthma were entered into the study on presenting to the emergency department. They were blindly randomized to receive one of three drug regimens: (1) inhaled furosemide (40 mg) (n=8); (2) inhaled metaproterenol (15 mg) (n=7); or (3) the combination of furosemide (40 mg) and metaproterenol (15 mg) (n=9). We measured FEV₁ at entry (time 0) and 15, 30, 45, and 60 min after inhalation of the individual drugs or the combination from a face mask nebulizer. At entry, the three groups did not differ significantly in age (mean ± SEM=37.5±3.6, 38.5±3.6, and 41.0 years, respectively; p=0.770), baseline FEV₁ (1.01±0.27, 1.04±0.27, and 1.25±0.14 L, respectively; p=0.620), or the theophylline levels (2.87±1.8, 7.39±2.8, and 5.29±2.6 µg/ml, respectively; p=0.498). Pretreatment and posttreatment potassium levels were similar among the three groups. Inhalation of furosemide alone resulted in a 14.9±10.5 percent change in FEV₁ percent from baseline, which was not statistically significant. In contrast, metaproterenol alone resulted in a 42.9±15.2 percent increase in FEV₁ percent (F ratio=6.226; p=0.0028). The combination of furosemide and metaproterenol resulted in a change in FEV₁ percent that was not statistically different compared with metaproterenol alone (FEV₁ percent=41.9±12 percent). No significant adverse effects occurred in any of the groups.

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Key words: asthma, bronchodilator, furosemide, metaproterenol

Recent reports have shown that when furosemide is administered as an aerosol to a patient with asthma, it can prevent or ameliorate the bronchoconstriction (asthmatic response) that is induced by a number of indirect challenges.1-14 These have included exercise, allergens, cold-air hyperventilation, metabisulfite, distilled water, adenosine 5’-monophosphate, lysine-aspirin, 4.5 percent sodium chloride, and fog.1-15 In contrast, furosemide does not exhibit a direct protective effect on the bronchoconstriction induced by histamine, methacholine, or prostaglandin F₂α.5,7,10,18,15 Of interest, one additional study has shown a statistically significant increase in the forced expiratory volume in 1 s (FEV₁) of asthmatics following provocative challenge with hyperventilation of cold, dry air.6 The other cited studies have not specifically evaluated the acute bronchodilating effects of furosemide. Thus, to our knowledge, the role of furosemide in the treatment of asthma exacerbations has not been studied.

Although the mechanism responsible for altering the asthmatic response in the above studies remains controversial, some investigators have postulated that this effect may be due to the diuretic’s ability to interfere with ion and water movement across airway epithelium.1-16 Others have argued that it is due to inhibition of inflammatory mediators, inhibition of carbonic anhydrase, and/or increased production of prostaglandin E₂.6,16 Regardless of how it works, it appears that inhalation of furosemide can alter the asthmatic response to certain types of airway challenges. As we have previously shown that many asthmatic patients with acute exacerbations do not consistently respond to conventional therapy with β-agonists17 or anticholinergics,18 the purpose of this study was to determine if there is a role for inhaled furosemide in the treatment of acute exacerbations of asthma.

METHODS

Twenty-four patients who presented to the Montefiore Medical Center emergency department with acute exacerbations of asthma were entered into this study. All patients had asthma as defined by the American Thoracic Society.19 To be eligible for the study, the patients had to be between 18 and 45 years old and their FEV₁ had to be less than 60 percent of predicted normal. If they were cigarette smokers, they had to have smoked less than 10 pack-years. Patients were excluded from the study if they had COPD as defined by the American Thoracic Society,19 clinical evidence of acute respiratory failure, any acute concomitant medical problems, were pregnant, or had received nebulizer treatments with β-agonist solutions in the previous 6 h. All par-

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Table 1—Patient Demographics* (n=24)

<table>
<thead>
<tr>
<th></th>
<th>Age, yr</th>
<th>FEV1, L</th>
<th>Theophylline, µg/ml</th>
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</thead>
<tbody>
<tr>
<td>Metaproterenol (n=8)</td>
<td>38.5 ± 3.6</td>
<td>1.04 ± 0.27</td>
<td>7.39 ± 2.8</td>
</tr>
<tr>
<td>Furosemide (n=7)</td>
<td>37.6 ± 3.6</td>
<td>1.01 ± 0.14</td>
<td>2.87 ± 1.82</td>
</tr>
<tr>
<td>Metaproterenol and furosemide (n=9)</td>
<td>41.0 ± 3.2</td>
<td>1.25 ± 0.14</td>
<td>5.29 ± 2.60</td>
</tr>
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</table>

*All values represent the mean ± SEM; All p values are <0.05.

Participating subjects signed a consent form as approved by our Institutional Review Board.

Patients were randomly assigned to receive one of three medication protocols: (1) metaproterenol sulfate solution (0.3 ml or 15 mg diluted to a final volume of 3 ml with 0.9 percent normal saline solution); (2) furosemide solution (40 mg) diluted to a final volume of 3 ml with 0.9 percent normal saline solution; or (3) metaproterenol sulfate solution (0.3 ml or 15 mg) combined with furosemide solution, 40 mg, diluted to a final volume of 3 ml with 0.9 percent normal saline solution.

Specifics of the protocol were as follows. First, baseline FEV1 was obtained. If the patients qualified for the study, they were randomly given one of the three study nebulizer solutions as described above. Spirometry was then performed at 15, 30, 45, and 60 min after complete inhalation of the drug (time 0). All spirometry was performed with a spirometer (Jones Datamate V Spirometer, Jones Medical Instrument, Oak Brook, Ill). Flow rates were measured in triplicate at 1-min intervals with the subject seated upright and the nose occluded. The best FEV1 from each set was included for data analysis. The spirometer was calibrated daily.

All medications were prepared, coded, and randomized by the pharmacy investigator participating in this study (D.L.). Both the physicians administering the medications and the patients receiving the nebulizer solutions were blinded as to which medications were nebulized during the study. The solutions were prepared daily, coded, and then given to the physician investigators to administer.

All medications were nebulized with a nebulizer (Hudson Jet-stream Nebulizer, Hudson; Wadsworth, Ohio) with a face mask fitted over the nose and mouth until the nebulizer was dry.

Prior to administering the nebulizer solutions, 5 ml of venous blood was obtained for baseline potassium and theophylline levels. At the termination of the study (time=60 min), a second potassium level was obtained.

During the course of the study, no other medications were administered, and hydration was oral and ad lib.

Data Analysis

Two-way analysis of variance and Duncan's multiple range test were used to compare the three drug regimens. The posttreatment improvement in FEV1 was expressed as percent improvement above baseline (time 0). A p value of less than 0.05 was considered to indicate statistical significance.

Results

Twenty-four patients were entered into this study. Eight patients received metaproterenol alone, seven received furosemide alone, and nine received the combination of metaproterenol and furosemide. Pertinent demographics for these patients are shown in Table 1. There were no statistically significant differences among three groups for the parameters noted. The patients were young (third and fourth decade) and had severe airway obstruction (mean entry FEV1, about 1 L). Furthermore, prestudy

![Graph](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21703/)

**Figure 1.** The FEV1 (percent baseline) vs time is shown for each of the drug regimens administered. Data are represented as mean ± SEM values.
medication use was not statistically significantly different among the three groups. All patients had used a metered-dose inhaler with a \(\beta\)-agonist before coming to the emergency department. The time to prior usage of the metered-dose inhaler ranged from a minimum of 1 h to a maximum of 6 h. For the group that received furosemide alone, three patients were using inhaled steroids and one was using oral steroids. In the group receiving metaproterenol alone, two patients were using inhaled corticosteroids and two patients were using oral corticosteroids. For the group receiving combination therapy, three patients were using inhaled corticosteroids and one patient was using oral corticosteroids.

Figure 1 shows the FEV\(_1\) (percent baseline) vs time for all three groups of patients. The patients who received inhaled furosemide alone achieved a maximum increase in FEV\(_1\) of 14.9 \(\pm\) 10.5 percent at 15 min. This improvement was not statistically significant (F ratio = 0.990; \(p = 0.4290\)). Furthermore, this trend toward an increase in FEV\(_1\) percent change from baseline was not sustained beyond 15 min, and by 45 min, the FEV\(_1\) was approximately at its baseline. For the patients who received metaproterenol alone, the maximum percent change in FEV\(_1\) was 42.9 \(\pm\) 15.2 percent and this improvement was sustained during the study. This improvement was statistically different than that for the group of patients receiving furosemide alone (F ratio = 6.226; \(p = 0.0028\), effect of drug over time by analysis of variance). Lastly, the combination of metaproterenol and furosemide resulted in an increase in FEV\(_1\) percent of 41.9 \(\pm\) 12 percent. This was not statistically significantly different from metaproterenol alone, but was again significant compared with furosemide alone (by Duncan’s Multiple Range Test for FEV\(_1\) percent by drug; data not shown), suggesting that the bronchodilator effect was due to the metaproterenol alone and that there was no synergy between the metaproterenol and furosemide.

Figure 2 demonstrates the best improvement in FEV\(_1\) (percent change from baseline) for each patient studied in each treatment arm of the protocol. Of note, only one patient had a large increase in FEV\(_1\) following inhalation of furosemide.

The pretreatment and posttreatment potassium levels are shown in Table 2. There were no significant differences demonstrated pretreatment or posttreatment for any of the patients. Furthermore, the potassium levels were not significantly different be-

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>Posttreatment</th>
<th>Mean Change</th>
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<tbody>
<tr>
<td>Metaproterenol</td>
<td>4.19 (\pm) 0.25</td>
<td>4.14 (\pm) 0.27</td>
</tr>
<tr>
<td>Furosemide</td>
<td>4.15 (\pm) 0.12</td>
<td>3.82 (\pm) 0.27</td>
</tr>
<tr>
<td>Metaproterenol and furosemide</td>
<td>4.09 (\pm) 0.35</td>
<td>3.66 (\pm) 0.13</td>
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*Values are mean \(\pm\) SEM potassium levels (\(\mu\)g/ml); F ratio = 0.590; \(p = 0.566\).
fore or after drug treatment among any of the groups.

No significant adverse effects occurred with any of the treatment medications and all 24 patients entered into the trial completed the study.

At the termination of the study, the patients were returned to the care of the emergency department physicians.

**Discussion**

Although inhaled furosemide has been shown to attenuate the bronchoconstriction that follows many types of provocative challenges in asthmatic subjects, our current study, which to our knowledge is the first to evaluate the efficacy of this drug in the setting of acute asthma, has failed to show any significant role for this drug.

Our trial compared inhaled furosemide (40 mg) alone with inhaled metaproterenol (15 mg), and the combination of both drugs nebulized together in a group of patients presenting to the emergency department with exacerbations of asthma. Our results demonstrated that furosemide alone resulted in a mean change in FEV₁ of 14.9 ± 10.5 percent, which was not statistically significant compared with baseline FEV₁ for the group that received it. Only one patient had a substantial increase in FEV₁ following inhalation of furosemide. Furthermore, the change in FEV₁ percent (compared with baseline) was less than the improvement noted for the group receiving metaproterenol alone (42.9 ± 15.2 percent). Combination therapy with both metaproterenol and furosemide did not result in any additional improvement in FEV₁ compared with metaproterenol alone, suggesting that combination therapy does not confer any additional benefit.

All of our patients had similar demographics, prior medication usage, and pulmonary function at entry into the study. Therefore, differences in responses to the medications cannot be attributed to differences in the degree of airway obstruction, theophylline levels, or patient population. We believe all the patients had similar capacities to improve and that the differences in their responses truly reflected differences in the treatments that were administered.

Although we studied a relatively small patient sample, we found no statistically significant effect of furosemide alone. We do, however, recognize that a large β-error can exist. To prove whether furosemide has more than a truly negligible effect would require 50 patients or more. However, we believe, that from a clinical point of view, the 15 percent improvement with furosemide alone is correctly characterized as being insignificant. Only one patient was noted to have a substantial individual improvement in FEV₁ while two others demonstrated a small improvement in FEV₁. Therefore, we conclude that clinically furosemide is not of significant benefit, but the small changes documented are of significant academic interest.

Previously published literature that evaluated furosemide in provocative challenge studies did not specifically evaluate the bronchodilator effects of the drug in the acute clinical setting. However, O’Donnell and coworkers performed provocative challenge studies with hyperventilation of cold, dry air in seven subjects who inhaled 80 mg of furosemide and they demonstrated a 14 percent increase in FEV₁ during exposure of the subjects to postnebulization challenge. Concomitant with this rise in FEV₁, the subjects also experienced a significant fivefold increase in urinary output.

The above study differs from ours in several important aspects. First, the study by O’Donnell and coworkers evaluated asthmatics with mild airway obstruction who had stable conditions and were being subjected to provocative challenge to induce asthma. They studied a small number of patients who demonstrated statistically significant increases in FEV₁, the clinical significance of which is questionable. In contrast, we studied a larger population of patients with acute, severe airway obstruction who did not have a significant bronchodilator response to furosemide compared with metaproterenol. Interestingly, the mean improvement in FEV₁ percent was almost identical in the two studies, but statistically it did not reach significance in our larger population of patients. The O’Donnell et al. study also used a larger dose of furosemide than our study used (80 mg vs 40 mg, respectively). However, this larger dose was accompanied by an impressive diuresis, making the use of this dosage impractical when treating patients with asthma exacerbations in the emergency department. Therefore, we do not believe that our current study bears repeating using larger dosages of furosemide.

In conclusion, our data show that inhaled furosemide is an ineffective treatment for asthma exacerbations as it produces only a small improvement in pulmonary function during acute bronchospasm. As previous literature has shown that it effectively ameliorates the bronchospasm that certain types of provocative challenge can induce, future work should primarily be directed toward defining the mechanism of action and the potential role for furosemide as a prophylactic agent.

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**References**

Inhaled Furosemide Is Not Effective in Acute Asthma (Karpe et al)