Albuterol Delivered by Metered-Dose Inhaler to Treat Acute Bronchitis

William J. Hueston, MD
Eau Claire, Wisconsin

Background. Previous research has suggested that cough associated with acute bronchitis is more likely to subside within 7 days when treated with albuterol than with an antibiotic. This study examines the effectiveness of aerosolized albuterol for the treatment of acute bronchitis in patients treated with erythromycin or placebo.

Methods. A double-blind, randomized placebo-controlled trial of albuterol delivered by metered-dose inhaler (MDI) was conducted in a primary care setting with healthy adult patients who presented with a productive cough of fewer than 30 days' duration. In addition to randomization for albuterol, patients were also randomized to receive erythromycin or placebo. Outcomes were assessed at follow-up after 7 days.

Results. Patients treated with albuterol MDI were less likely to be coughing after 7 days of treatment than were patients using a placebo inhaler (61% still coughing vs 91%, $P=.02$). When analysis was stratified by cigarette smoking status and the use of erythromycin, the differences observed between albuterol MDI patients and controls persisted.

Conclusions. Albuterol appears to reduce the likelihood that patients with acute bronchitis will be coughing after 7 days following initiation of treatment. This effect appears to be independent of cigarette smoking or the concomitant use of antibiotics.

Key words. Cough; bronchitis; acute disease; albuterol; family practice. (*J Fam Pract* 1994; 39:437-440)

Acute bronchitis is one of the most common problems encountered by primary care physicians.[1-3] This disorder is usually a self-limited illness that resolves spontaneously without therapy. Although antibiotic therapy is frequently used for patients with acute bronchitis,[4,5] there is only scant evidence that patients receive significant clinical benefit from any of the antibiotics previously evaluated.[6-9]

Because of the similarity in pulmonary function test results in patients with acute bronchitis and those with asthma,[10,11] treatment with bronchodilating agents may be a more effective therapy than antibiotics for acute bronchitis. Initial studies evaluating this strategy suggested that, when compared with patients treated with erythromycin, patients treated with bronchodilators had more prompt resolution of their symptoms.[12,13] This study evaluates aerosolized albuterol delivered by a metered-dose inhaler to further explore the potential effectiveness of bronchodilators for the treatment of acute bronchitis symptoms.

Methods

The sample was drawn from adult patients aged 18 to 65 who attended two community-based family practice centers in Kentucky and Wisconsin. Patients who presented with a productive cough of less than 30 days' duration and who had no signs of pneumonia, as determined by a negative chest radiograph or by the clinical judgment of their physicians, were initially eligible for inclusion. Patients who had any history of asthma, chronic obstructive pulmonary disease, or cardiac disease were excluded, as were all patients who were pregnant or allergic to either of the study medications, and those who had received antibiotics for any reason in the previous 2 weeks. Patients who had previously had bronchitis were not excluded.

After meeting the inclusion and exclusion criteria for

the project, patients were informed of the study protocols and gave informed consent prior to enrollment. Patients were then given a packet containing an inhaler and 40 opaque capsules that contained either erythromycin (250 mg) or a lactose placebo. Inhalers contained either active albuterol (Ventolin inhaler, Allen & Hanburys, Research Triangle Park, NC) or an inert placebo (obtained from Allen & Hanburys). Before distribution to the study participants, the canisters containing the inhaled drug or placebo had been removed from their plastic containers and opaque tape had been placed around the canister to disguise its contents. Canisters were then randomly returned to the plastic containers so that the color of the outside container was not indicative of the medication in the canister. Containers were then covered with a medication label that noted the study number and gave instructions for use. Written instructions on the proper use of an inhaler were given to all patients, and an office nurse reviewed the instructions with the patients before they left the office. Based on the contents of the study packets, four groups of patients were defined: albuterol and erythromycin, albuterol and placebo, erythromycin and placebo, and two placebos.

Examining physicians completed an initial data form, listing demographics and features of the presenting illness for each patient. During the 7 days of therapy, patients recorded in a diary the presence of cough or night cough, ability to perform their normal work, and general level of well-being. Patients also recorded any side effects and the use of other over-the-counter (OTC) medications. After 7 days of therapy, patients returned for follow-up, their diaries were collected, and they were reexamined. Patients had been instructed to bring their unused capsules to the follow-up visit so that the remaining pills could be counted in order to estimate patient compliance. When patients did not attend their scheduled follow-up appointment, they were contacted by telephone, reminded of their appointment, and examined the following day.

Data analysis consisted of the chi-square test for categorical variables. When categorical variables were stratified for analysis, comparisons were performed using a Mantel-Haenszel statistic. Continuous variables were analyzed with Student's t test when groups had similar variances, and with the Kruskal-Wallis H test when variances differed. Statistical significance was defined as an $\alpha < .05$.

The study was originally designed to enroll 132 patients and compare the four groups noted above. Included in the design was an evaluation of outcomes after one third and after two thirds of the patients completed the trial. Because of statistically significant results found in the primary study outcome (resolution of cough), the study was suspended after 46 patients completed the study.

Table 1. Patient Characteristics at the Time of Enrollment in a Study of the Effectiveness of Albuterol Administered by Metered-Dose Inhaler to Treat Acute Bronchitis

Variable	Albuterol Group (n=23)	Control Group (n=23)	P Value
Male, %	48	30	NS
Mean age (SD), y	32.9 (12.7)	36.9 (11.4)	NS
Smokers, %	43	57	NS
Mean duration of cough (SD), d	8.6 (6.6)	8.7 (5.2)	NS
Night cough present, %	83	96	NS
Fever over 39°C, %	13	21	NS
Abnormal lung examination, %	52	52	NS

Results

Using the inclusion and exclusion criteria detailed above, 46 patients completed the study. Twenty-three patients were assigned to albuterol metered-dose inhalers (MDI) and 23 received placebo inhalers. All patients who were initially enrolled completed follow-up within 8 days of starting the study medications.

Compared with control patients, those who were randomized to albuterol MDIs were similar in age, sex, and cigarette use (Table 1). In addition, clinical aspects of their disease (duration of cough, presence of a night cough, and presence of a fever or an abnormal lung examination) were not significantly different between the albuterol and control groups. When abnormalities were present on lung examination, the most common finding in both groups was wheezing (52% of patients in albuterol group and 30% of patients in the control group).

When patients returned for follow-up after 7 days of treatment, there was no difference between patients in the albuterol group and patients in the control group in the rate of compliance with therapy as defined by the number of capsules returned after 1 week (3.4±5.3 vs 2.2±3.2, respectively, P=NS).

After 7 days of therapy, a statistically significant decrease in the percentage of patients who were still coughing was noted for the albuterol group as compared with the control group (61% vs 91%, P=.02). Among patients treated with albuterol, there was no statistically significant difference in the percentage who were cough-free based on initial lung examination after 7 days (36% resolved in those with normal initial examinations vs 42% resolved in those with initial abnormalities, P=NS). Examination of other symptoms showed no significant differences be-

Table 2. Outcomes After 7 days of Treatment with Albuterol Metered-Dose Inhaler vs Placebo

Outcome	Albuterol Group (n=23)	Control Group (n=23)	P Value
Still coughing, %	61	91	.02
Productive cough present, %	57	48	NS
Night cough persists,* %	26	45	NS

*Analysis limited to patients who initially presented with night cough.

tween patients treated with albuterol and those treated with placebo (Table 2).

Four of the 23 (17%) patients in both groups continued to have lung abnormalities after 7 days of therapy, and 2 (9%) of the patients in both groups had side effects attributed to the study medications. While an equal number of patients in each group experienced side effects that they attributed to the medication, none in either group stopped taking their medication because of side effects (Table 2). Symptoms diaries showed no significant differences between the groups with respect to the amount of time required for their level of well-being to improve. By day 4, however, patients treated with albuterol were more likely to return to work (78% vs 52%, P=.05). There was no difference in the percentage of patients in the albuterol and control groups who used OTC medications (30% vs 26%, P=NS). The use of OTC medications was limited to acetaminophen or ibuprofen (four patients), cough syrups containing dextromethorphan (three patients), and antihistamine/decongestants (six patients). None of the patients reported using any OTC medications containing theophylline or aerosolized epinephrine.

Because of the possibility that differences in the percentage of patients in the two groups who used erythromycin could have influenced the observed outcomes, further analysis was performed with stratification by erythromycin use. When this was done, patients in the albuterol group continued to show a statistically significant decrease in coughing at 7 days (Mantel-Haenszel statistic=4.30, P=.04) and returned to work (Mantel-Haenszel statistic=4.27, P=.04) as compared with controls.

The outcomes were also stratified by smoking status. This analysis was conducted on the premise that all patients who use cigarettes may have some degree of obstructive lung disease, and thus, smokers would be more likely to improve with albuterol use. Although the number of patients in each group was small, no difference in response rates was seen in smokers as compared with nonsmokers (69% vs 50% still coughing) in the albuterol group.

Discussion

These results suggest that patients with acute bronchitis who were treated with MDI-delivered albuterol were more likely than patients treated with the placebo inhaler to have their cough resolve within 7 days of treatment and to return to work early. Although the number of subjects in each group was small, an improvement in cough was noted in both smokers and nonsmokers treated with albuterol and either erythromycin or placebo.

This study confirms the findings of a previous study that compared the effects of oral albuterol to those of erythromycin in adults with acute bronchitis.[11] In the previous study, an increased percentage of patients treated with albuterol experienced resolution of their cough within 7 days as compared with patients treated with erythromycin. However, 35% of patients treated with oral albuterol reported side effects and 10% discontinued the medication for this reason.[12] The results of the current study demonstrate that MDI-delivered albuterol is just as effective as and better tolerated than oral albuterol. This study also included a randomized group of patients treated with antibiotics in combination with albuterol and found that the concomitant use of these two medications did not appear to affect the short-term outcomes of patients.

Previous evidence has suggested that the symptoms of acute bronchitis represent transient bronchial edema and spasm. The importance of bronchospasm in acute bronchitis has been suggested by prior pulmonary function tests in patients with this illness.[10,11] Furthermore, investigators have noted an association between recurrent acute bronchitis and asthma, suggesting that patients with symptomatic acute bronchitis are prone to bronchospastic disease.[14,16] The short-term effectiveness of albuterol in patients with acute bronchitis suggests that symptoms from this disorder are caused primarily by bronchospasm and that the most effective treatments for this disorder are likely to be bronchodilators.

This study also suggests that antibiotic therapy added to bronchodilators has little effect on the symptoms of acute bronchitis. Although antibiotics are not recommended by experts for acute bronchitis,[16,17] antibiotics are still commonly prescribed by primary care physicians.[4,5] While some evidence suggests that antibiotic use in patients identified with *Mycoplasma* infections can be useful,[18] it appears from these data that MDI-delivered albuterol is a more effective and safer treatment for patients with acute bronchitis. More research will be needed

to determine whether antibiotic therapy results in improved outcomes in certain patient populations treated with bronchodilator agents.

Although the results of this study are encouraging, the conclusions should be viewed within the limitations of the methods. First, the definition of acute bronchitis is vague.[19] While the clinical characteristics of the patients randomized to the two intervention groups appeared equal, the broad definition of acute bronchitis employed in this study may have masked important differences between these two groups. Second, the small number of subjects enrolled in the study does not allow suitable power to compare variables other than the primary outcome of cough. It is possible that small differences between the groups that were not statistically significant would reach significance with a larger patient population. Finally, this study was limited to healthy adults and relied on outcomes self-reported by these persons. It is unclear how effective albuterol might be for acute bronchitis in children or adults with underlying pulmonary disorders. Further evaluation of bronchodilators in patients with acute bronchitis with a focus on special populations, such as smokers, children, and patients with underlying pulmonary problems or recurrent bronchitis, would help define the most effective use of this treatment modality.

Although this study did not employ any objective measures of pulmonary function, such as peak flows, the clinical outcomes used are indicative of desired endpoints by most patients with bronchitis. While it might be convincing to demonstrate reversible airway obstruction in these individuals, the most clinically relevant outcomes are probably those that relate to patient function, which include ability to work and freedom from cough. For these outcomes, only patient self-report was available. It is possible that the results could be biased by patients reporting improved outcomes in order to please their physicians; however, since patients were blinded to their medication, both placebo and albuterol results would have been equally affected and no bias favoring the treatment group would have resulted.

Acknowledgments

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