

THE EFFICACY OF NEBULIZED ALBUTEROL/IPRATROPIUM BROMIDE VERSUS ALBUTEROL ALONE IN THE PREHOSPITAL TREATMENT OF SUSPECTED REACTIVE AIRWAYS DISEASE

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ABSTRACT

Objective. Ipratropium bromide has demonstrated efficacy when added to albuterol for the treatment of reactive airways disease (RAD). Its prehospital use has not been explored. **Methods.** A before-and-after design was used. Prehospital and emergency department (ED) medical records were examined retrospectively six months before and six months after institution of a new protocol, which allowed the addition of ipratropium bromide to all nebulized treatments with albuterol. Primary outcome measures included: changes in vital signs (heart rate, respiratory rate, oxygen saturation), clinical improvement as assessed by paramedics, and admission rates. **Results.** A total of 371 patients were included ($n = 192$ albuterol alone, $n = 179$ ipratropium/albuterol). There was no statistically significant difference between groups with regard to the change in heart rate, respiratory rate, or oxygen saturation. In addition, there was no difference in the proportion of patients with clinical improvement or deterioration as assessed by paramedics. There was no statistically significant difference in the admission rate from the ED except in the subgroup of patients using a metered-dose inhaler at the time of illness. Of note, more than one-third (133/371) of the patients were ultimately determined to have a diagnosis other than RAD, the majority of whom were diagnosed as having cardiac disease. **Conclusions.** The addition of ipratropium bromide to albuterol for the prehospital treatment of RAD does not appear to result in clinical outcome improvements. A substantial number of patients enrolled in the study were diagnosed as having cardiac disease. **Key words:** albuterol; ipratropium; reactive airways disease; cardiac disease.

PREHOSPITAL EMERGENCY CARE 2005;9:386-390

Acute exacerbations of reactive airways disease (RAD) are commonly encountered in the prehospital environment. Albuterol is commonly used to treat mild-to-moderate RAD, with subcutaneous injection of epinephrine and ventilatory support reserved for the most severe attacks. Ipratropium bromide is a quater-

nary ammonium compound that is poorly absorbed from the lung or gastrointestinal tract, giving it a favorable therapeutic range with few side effects.¹ The onset of action can be as soon as 10–15 minutes, with a peak effect occurring at one to two hours and efficacy for up to eight hours, depending on the administered dose.² Ipratropium acts as a nonselective antagonist at muscarinic receptors, decreasing mucus secretion and producing large-airway bronchodilation.^{3,4}

A relative decline in the number and sensitivity of adrenergic receptors has been documented with advancing age.⁵ This results in a theoretical advantage to anticholinergic agents, such as ipratropium bromide, in older patients. This likely explains the role of ipratropium bromide in the treatment of chronic obstructive pulmonary disease (COPD), which is typically a disease of older patients. In addition, ipratropium bromide may offer potential efficacy via a different mechanism in patients who respond incompletely to adrenergic agonists such as albuterol.

Many investigators have attempted to document additional efficacy with the addition of nebulized ipratropium bromide to albuterol. In pediatric patients, improvements in both pulmonary function tests (PFTs) and hospital admissions rates suggest an advantage to this combination.^{6–8} In adults, however, the data have been somewhat inconsistent and difficult to interpret. While some studies reveal faster response rates, improved PFTs, and lower admission rates, other studies show no difference.^{9–19} Even when specific subgroups of patients are studied, the results have been inconsistent, possibly due to inconsistencies in the times at which posttreatment variables were measured.^{11,13,15–21} Two meta-analyses suggest potential benefit with the addition of ipratropium bromide to albuterol in the emergency department (ED).^{22,23} No previous studies have evaluated the prehospital administration of ipratropium. Here we take advantage of a natural experiment to explore the efficacy of nebulized ipratropium bromide when added to albuterol versus albuterol alone in the treatment of suspected RAD in adults. This study has relevance to emergency medical services (EMS) systems considering the addition of ipratropium to their paramedic scope of practice. If the addition of ipratropium is determined not to have additional benefit over albuterol alone, EMS systems may decide to simplify the prehospital RAD treatment regimen and decrease unnecessary costs. In addition, we

Received February 18, 2005, from the Department of Emergency Medicine (DPD, TCC, GMV) and the School of Medicine (CW), University of California, San Diego, San Diego, California. Revision received May 5, 2005; accepted for publication May 9, 2005.

Presented at the National Association of EMS Physicians annual meeting, Tucson, Arizona, January 2004.

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doi:10.1080/10903120500255404

perform separate analyses of several subgroups to help identify patients who might benefit from ipratropium over albuterol alone and to determine whether certain patients, such as those ultimately determined to have a cardiac etiology for their dyspnea, might actually be harmed by the administration of a chronotropic agent that might increase myocardial oxygen demand.

METHODS

Study Design

We used a before-and-after design to explore the additional efficacy afforded by nebulized ipratropium bromide when added to albuterol in the treatment of suspected RAD. All data were collected retrospectively using EMS and ED records from January 1, 2000, to December 31, 2000. Waiver of informed consent was granted from our Institutional Human Resources Protection Program.

Subjects

We included all adult (age 18 years or more) prehospital patients transported to the University of California, San Diego (UCSD) ED who were treated with nebulized albuterol or albuterol/ipratropium bromide for suspected RAD. The UCSD ED is an urban, university-affiliated facility receiving approximately 40,000 annual visits.

Treatment Protocol

The San Diego County paramedic treatment protocol for adult patients with acute dyspnea includes the following: 1) three-lead electrocardiogram (ECG) and pulse oximetry, 2) placement of an intravenous catheter as needed, 3) administration of oxygen indicated, 4) administration of nebulized bronchodilator therapy (maximum of two doses) if RAD is suspected, 5) sublingual administration of nitroglycerin for suspected angina, 6) subcutaneous administration of epinephrine as indicated (<55 years of age and no cardiac history) if RAD is suspected, and 7) endotracheal intubation as indicated. Prior to July 1, 2000, nebulized bronchodilator therapy consisted of albuterol alone (2.5 mg/treatment); after July 1, 2000, nebulized bronchodilator therapy included both albuterol (2.5 mg/treatment) and ipratropium bromide (0.5 mg/treatment). Nebulizer treatments are administered using pressurized oxygen.

Data Collection

A single reviewer abstracted all data from EMS and ED records. Patients in the "albuterol only" group (January 1, 2000–June 31, 2000) and in the "albuterol/ipratropium" group (July 1, 2000–December

31, 2000) were identified using the QANet, a county database of all prehospital encounters. The QANet was also used to abstract the following data for all patients: age, gender, prenebulizer vital signs, postnebulizer vital signs, treatments administered, and any record of clinical response to therapy. The ED record was used to abstract the following data: medical history of asthma or COPD, use of a metered-dose inhaler (MDI) prior to transport, ED diagnosis, and ultimate disposition.

The primary outcome measure was the need for hospital admission, comparing patients receiving albuterol alone with those receiving albuterol and ipratropium bromide. A power calculation revealed 80% power ($\alpha = 0.05$) to detect a 15% absolute difference in the rates of admission. This is roughly equivalent to values reported in a previous meta-analysis documenting a relative risk of 0.75 for admission with the use of ipratropium with albuterol.²³ With an "albuterol only" admission rate of approximately 50%, this would result in an absolute admission rate difference of about 13%, which is consistent with our power calculation.

In addition, comparisons were made between the groups with regard to demographics, past medical history, heart rate, blood pressure, respiratory rate, oxygen saturation (SaO_2), and paramedic assessment of clinical status before and after treatment (when recorded). The two groups were also compared with regard to the percentage of patients with an improvement in SaO_2 greater than 2%. This threshold value was selected because it represents the measurement precision of the SaO_2 and was felt to be clinically relevant. Finally, patients were stratified by past medical history and ED diagnosis to explore differences in vital signs or the rate of admission.

Statistical Analysis

Data were analyzed with Microsoft Excel 9.0 (Microsoft Corp., Redmond, WA) and SPSS 11.0 for Windows (SPSS Inc., Chicago, IL). Changes in vital signs were evaluated with repeated measures analysis of variance (ANOVA) with two between-subjects factors (drug therapy, age) and one within-subjects factor (time) after assessing normality of distribution. For patient subgroups, a univariate ANOVA was used for vital signs. The number of patients with an SaO_2 increase of greater than 2% and the number of patients identified by paramedics as improving were evaluated using logistic regression. Mean values \pm standard deviation were calculated for continuous variables. Statistical significance was assumed for $p < 0.05$.

RESULTS

A total of 192 patients were included in the "albuterol only" cohort and 179 patients were treated in the "albuterol/ipratropium" cohort. Baseline characteristics

TABLE 1. Demographics and Past Medical History (PMH) for the "Albuterol Alone" and "Albuterol + Ipratropium" Cohorts

Parameter	Albuterol Alone (n = 192)	Albuterol + Ipratropium (n = 179)	p-value
Gender—male	107 (56%)	101 (56%)	0.893
Age—mean	53.0 yr	53.4 yr	0.849
PMH			
Asthma	88 (46%)	83 (46%)	0.918
COPD	59 (31%)	52 (29%)	0.630
MDI use at home	98 (51%)	89 (50%)	0.799
None/unknown	53 (28%)	41 (23%)	0.298
Dx RAD in ED	124 (52%)	114 (48%)	0.857

COPD = chronic obstructive pulmonary disease; MDI = metered-dose inhaler; Dx RAD in ED = diagnosis of reactive airways disease in the emergency department.

were similar between the two groups (Table 1). In addition, there was no statistically significant difference between the cohorts with regard to other prehospital treatments administered (Table 2).

There was no statistically significant difference between the two groups with regard to pre- and postnebulizer values for heart rate, blood pressure, respiratory rate, or SaO₂. In addition, there was no statistically significant difference between the groups with regard to the change in these values. Furthermore, there was no statistically significant difference between the groups with regard to paramedic clinical assessments following nebulizer treatments. These data are displayed in Table 3. With regard to the primary outcome measure, there was no statistically significant difference in the rate of admission between the "albuterol only" cohort and the "albuterol/ipratropium" cohort (Table 4).

Patients were then stratified based on past medical history and ED admission diagnosis, with no statistically significant difference observed with regard to any of the outcome measures (Table 5). The one exception was a 4-mm Hg decrease in systolic blood pressure for the "albuterol only" cohort versus a 7-mm Hg decrease in the "albuterol/ipratropium" cohort, which likely has little clinical significance. Of note, approximately one-third of all patients were ultimately diagnosed as having a cardiac etiology for their dyspnea, including both

TABLE 2. Prehospital Treatments for the "Albuterol Alone" and "Albuterol + Ipratropium" Cohorts

Intervention	Albuterol Alone (n = 192)	Albuterol + Ipratropium (n = 179)	p-value
Intubation	1 (1%)	3 (2%)	0.282
BVM ventilation	0 (0%)	3 (2%)	0.159
SQ epinephrine			
Prior to 1st neb	3 (2%)	4 (2%)	0.635
After 1st neb	10 (5%)	6 (3%)	0.379

BVM = bag-valve-mask; SQ = subcutaneous; neb = nebulization.

TABLE 3. Change in Vital Signs and Overall Clinical Status for the "Albuterol Alone" and "Albuterol + Ipratropium" Cohorts

Parameter	Albuterol Alone (n = 192)	Albuterol + Ipratropium (n = 179)	p-value
Heart rate (beats/min)			
Pre	112	113	
Post	109	107	
Change	-3	-6	0.474
Blood pressure (mm Hg)			
Pre	149	147	
Post	142	137	
Change	-7	-10	0.523
Respiratory rate (breaths/min)			
Pre	29	32	
Post	29	28	
Change	0	-4	0.055
SaO ₂ (%)			
Pre	88	89	
Post	96	97	
Change	+8	+8	0.581
SaO ₂ increase >2% (%)	65 (34%)	76 (43%)	0.108
Improved clinical status (%)	65 (34%)	59 (33%)	0.944

SaO₂ = oxygen saturation.

acute coronary syndrome and congestive heart failure (CHF).

DISCUSSION

Here we compare patients with suspected RAD receiving prehospital nebulized albuterol before and after ipratropium bromide was added to the regimen. No statistically significant difference was observed in the rate of admission or with regard to any of the physiologic parameters included in this analysis. In addition, we were unable to identify a subgroup of patients benefiting from the addition of ipratropium despite stratification of patients by ED diagnosis or past medical history. Of note, about a third of patients suspected of having acute RAD in the field were ultimately diagnosed as having a cardiac etiology for their dyspnea.

Previous hospital-based studies suggest several indications for the use of inhaled ipratropium bromide in the treatment of RAD. Patients with COPD appear to benefit from the daily administration of

TABLE 4. Emergency Department Dispositions for the "Albuterol Alone" and "Albuterol + Ipratropium" Cohorts

Disposition	Albuterol Alone (n = 192)	Albuterol + Ipratropium (n = 179)	p-value
Admitted	102 (53%)	100 (56%)	0.596
Discharged	83 (43%)	74 (41%)	0.713
Left AMA	7 (4%)	5 (3%)	0.643
Expired	0 (0%)	0 (0%)	0.972

AMA = against medical advice.

TABLE 5. Changes in Vital Signs and Emergency Department (ED) Disposition for the “Albuterol Alone” and “Albuterol + Ipratropium” Cohorts, with Patients Stratified by ED Diagnosis and Metered-Dose Inhaler (MDI) Use

Parameter	Hx Asthma			Hx. COPD			MDI Uses			Dx RAD in ED		
	Alb (n = 88)	Alb/Ip (n = 83)	p	Alb (n = 59)	Alb/Ip (n = 52)	p	Alb (n = 98)	Alb/Ip (n = 89)	p	Alb (n = 124)	Alb+Ip (n = 114)	
Heart rate (beats/min)	0	+11	0.195	0	-6	0.880	+2	+10	0.532	+2	+4	0.463
SBP (mm Hg)	-4	-7	0.046	-10	-15	0.936	-5	-16	0.574	-3	-10	0.635
RR (breaths/min)	0	+3	0.305	-1	+1	0.562	0	+1	0.847	0	+2	0.693
↑SaO ₂ > 2% (%)	+6	+5	0.557	+8	+6	0.887	+6	+5	0.115	+6	+6	0.430
Admission (%)	39	49	0.156	66	60	0.480	41%	52%	0.136	46%	49%	0.626

Hx = history; COPD = chronic obstructive pulmonary disease; Dx RAD = diagnosis of reactive airways disease; Alb = albuterol; Alb/Ip = albuterol with ipratropium; SBP = systolic blood pressure; RR = respiratory rate; ↑SaO₂ = increase in oxygen saturation.

ipratropium bromide, possibly due to its effect on decreasing respiratory secretions and the relative increase in cholinergic versus adrenergic receptors with advancing age.^{3-5,23} It is less clear, however, whether patients with acute exacerbations of COPD receive additional benefit from nebulized ipratropium bromide over albuterol alone.^{11,13,15-19,24} In addition, ipratropium appears to benefit young persons who have asthma, with previous studies documenting improvements in vital signs, PFTs, and ultimate disposition with ipratropium added to nebulized albuterol therapy.^{6-8,25-27} The routine use of ipratropium in the adult patient with an acute exacerbation of RAD is less clear, with multiple studies demonstrating conflicting results.^{9-19,28-30} The variability in outcomes may be related to the use of surrogate endpoints measured at variable times following the administration of nebulized medication.^{20,21}

It is also notable that about a third of patients enrolled with suspected RAD were ultimately diagnosed as having a cardiac etiology for their symptoms. The ability of CHF to produce “cardiac asthma” is well established; however, the administration of chronotropic medications and failure to administer aspirin and nitroglycerin to a patient with possible ischemia are concerning. Fortunately, the heart rate did not increase across all subjects with either regimen. In addition, bronchodilators may be beneficial in “wheezing” patients, regardless of the etiology of symptoms.

LIMITATIONS

These data must be viewed in light of the study limitations. This was a retrospective chart review, and patients were not randomized to receive nebulized albuterol alone or in combination with ipratropium. We were unable to detect differences in the two cohorts; however, there may have been some selection bias as a result of the design. We also included all patients suspected of having acute exacerbations of RAD, resulting in a somewhat heterogeneous population and potentially obscuring a treatment effect of ipratropium. Subgroup analysis did not identify a population that would have benefited from the addition of ipratropium, and

prehospital personnel would not have access to ED diagnoses, making such an identification clinically irrelevant. In addition, the retrospective design resulted in missing variables. This was most notable with regard to paramedic assessments of improvement following nebulizer treatment. This was, however, the most subjective variable and highly subject to bias. Furthermore, we did not examine treatments in the ED, making it difficult to ascribe any differences in outcome to the prehospital use of ipratropium alone. We also were unable to measure pre- and posttreatment PFTs, which may be more sensitive in identifying a treatment effect of ipratropium. With regard to our EMS system, most transport times are relatively short, and a positive effect of ipratropium might be observed with longer transport times.

Our relatively small sample size represents another limitation. A power calculation was performed for the main outcome measures, but our ability to detect differences among subgroups was limited. Larger studies may ultimately reveal a population that benefits from prehospital use of ipratropium. We did not include pediatric patients in this analysis. Existing evidence supports the routine use of ipratropium in children with suspected RAD.⁶⁻⁸ We decided to limit this analysis to adults to focus on a patient group in whom the use of ipratropium is more controversial and for whom the misuse—as with cardiac-related dyspnea—might carry more significant consequences.

Finally, we considered hospital admission as an endpoint but did not attempt to determine the exact decision making involved in the disposition. For example, it is theoretically possible that one or more cardiac patients were admitted as a result of anginal symptoms induced by ipratropium or the physician perception that the preceding ipratropium administration warranted inpatient observation. This would have artificially inflated the admission rate for the ipratropium group. We did not, however, observe a significant increase in heart rate following ipratropium administration, and there was no difference between cohorts even when considering the subgroup of patients ultimately diagnosed as having RAD.

CONCLUSIONS

We performed a before-and-after study comparing two cohorts of prehospital patients with suspected RAD and receiving nebulized albuterol, with and without ipratropium bromide. There was no difference between the groups with regard to changes in vital signs, clinical improvements, and ED disposition. This suggests no additional benefit to ipratropium when added to nebulized albuterol in the prehospital environment. About a third of patients were ultimately diagnosed as having a cardiac etiology for their dyspnea, suggesting that the prospective identification of patients with acute RAD by paramedics is difficult.

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