Utilization of Bronchodilators in Ventilated Patients Without Obstructive Airways Disease

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OBJECTIVE: To examine physician practice in, and the costs of, prescribing inhaled bronchodilators to mechanically ventilated patients who do not have obstructive lung disease. METHODS: This was a prospective cohort study at 2 medical intensive care units at 2 tertiary-care academic medical centers, over a 6-month period. Included were the patients who required ≥ 24 hours of mechanical ventilation but did not have obstructive lung disease. Excluded were patients who had obstructive lung disease and/or who had undergone > 24 hours of mechanical ventilation outside the study intensive care units. RESULTS: Of the 206 patients included, 74 (36%) were prescribed inhaled bronchodilators without clear indication. Sixty-five of those 74 patients received both albuterol and ipratropium bromide, usually within the first 3 days of intubation (58 patients). Patients prescribed bronchodilators were more hypoxemic; their mean P_{aO_2}/F_{IO_2} ratio was lower (188 mm Hg versus 238 mm Hg, p = 0.004), and they were more likely to have pneumonia (53% vs 33%, p = 0.007). The mean extra cost for bronchodilators was $449.35 per patient. Between the group that did receive bronchodilators and the group that did not, there was no significant difference in the incidence of ventilator-associated pneumonia, tracheostomy, or mortality. The incidence of tachyarrhythmias was similar (15% vs 22%, p = 0.25). CONCLUSION: A substantial proportion of mechanically ventilated patients without obstructive lung disease received inhaled bronchodilators. *Key words: inhaled bronchodilators, mechanical ventilation, obstructive lung disease, albuterol, ipratropium bromide, intubation.* [Respir Care 2007;52(2):154–158.

Introduction

Bronchodilators are an important adjunctive therapy in the treatment of patients with obstructive lung disease who require mechanical ventilation. The benefit of bronchodilators in mechanically ventilated patients *without* obstructive lung disease is unclear.[1] Possible benefits of β agonists include enhanced mucociliary clearance,[2] optimization of lung mechanics,[3–5] decreased work of breathing,[6] and clearance of pulmonary edema.[7–11] However, β agonists may be associated with tachycardia, atrial and ventricular tachyarrhythmias, and metabolic derangements, including hypokalemia.[12–14] Benefits of ipratropium bromide are less clear, although it may decrease mucus hypersecretion. Bronchodilators are associated with higher cost in terms of pharmacy acquisition costs and nursing and respiratory therapist time.

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Our objective in this study was to examine physician practice in, and the costs of, prescribing inhaled albuterol

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and ipratropium bromide to patients who require more than one day of mechanical ventilation but who do not have a clear indication for these drugs.

Methods

Patient Population

All mechanically ventilated patients in the medical intensive care units (ICUs) at our 2 tertiary-care academic medical centers were screened for enrollment over a 6-month period in 2004. Patients were eligible if they required mechanical ventilation for > 24 hours; they were excluded if they had clinical evidence of obstructive lung disease or had undergone mechanical ventilation for > 24 hours outside the study ICUs. We defined clinical evidence of obstructive airways disease as: (1) documented history of asthma or chronic obstructive airways disease, (2) presence of wheezing noted on admission to the medical ICU, or (3) ongoing out-patient therapy with a bronchodilator. Subjects were enrolled at the time of intubation. The study was approved by both institutions' medical research reviews boards, which waived informed consent because the study only involved collection of existing medical information.

Data Collection

Baseline characteristics were obtained on enrollment into the study or extracted from the time of ICU admission. We then prospectively collected information regarding bronchodilator administration, presence of pneumonia or acute respiratory distress syndrome (ARDS), tachyarrhythmias, hours of tachycardia (defined as heart rate > 110 beats/min) per day, amount of potassium replacement, and ventilator time over the duration of the patient's mechanical ventilation. Pneumonia was defined as the presence of a new or progressive pulmonary infiltrate in association with fever, leukocytosis, and/or purulent tracheobronchial secretions.[15] ARDS was defined per the 1994 American-European Consensus Conference on ARDS.[16] Clinically probable ventilator-associated pneumonia was defined as new or progressive pulmonary infiltrates and ≥ 2 of:

1. Temperature > 38.0°C
2. Purulent endotracheal aspirate
3. Leukocytosis[17]

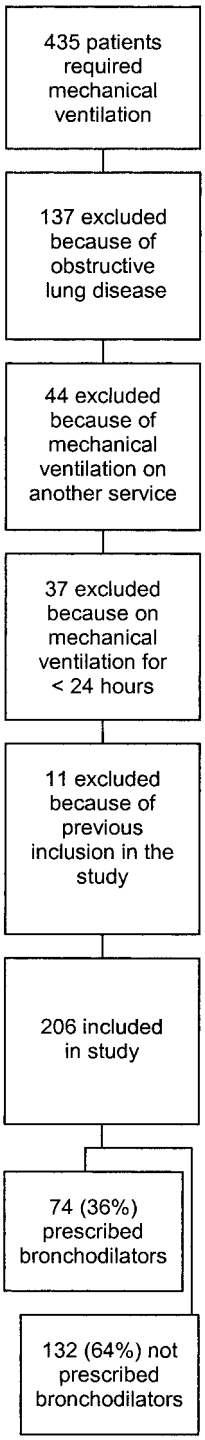

Fig. 1. Study enrollment.

Our primary outcome was the incidence of bronchodilator administration. Major secondary outcomes of interest were incidence of tachyarrhythmias and extra cost attributable to bronchodilator administration. Bronchodilators were administered via metered-dose inhaler, and we measured the number of individual inhalations per patient.

The authors report no conflicts of interest related to the content of this paper.

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Cost at one study center was based on pharmacy acquisition cost of the drug ($11.06 for albuterol and $28.90 for ipratropium bromide) plus the cost of respiratory therapist administration ($3.34 per administration). Cost at the other center was based on pharmacy acquisition cost ($3.20 for albuterol and $53.01 for ipratropium bromide) plus the cost of nursing administration ($8.17 per administration).

Statistical Analysis

The incidence of bronchodilator administration is presented as a percentage. Bivariate analysis of normally distributed continuous variables was via Student's *t* test. Nonnormal variables were analyzed via Wilcoxon's rank-sum test. Bivariate analysis of categorical variables was via Pearson's chi-square test or Fisher's exact test.

Results

Subjects

During the 6-month study period, 435 patients who required mechanical ventilation were admitted to the medical ICUs of the 2 hospitals (Fig. 1). Of those 435 patients, 37 were excluded because they were mechanically ventilated for < 24 hours, 44 were excluded because they were mechanically ventilated outside of the study ICUs for > 24 hours, 137 were excluded because of clinical evidence of obstructive airways disease, and 11 were excluded because they were intubated more than once during the 6-month study period (though enough time had passed between their intubations that they were not considered failed extubations). Thus, a total of 206 patients without obstructive lung disease required mechanical ventilation for > 24 hours. Of these 206 patients, 74 (36%) were prescribed inhaled albuterol and/or ipratropium bromide during mechanical ventilation: 30 at one center, and 44 at the other center. With 58 of those 74 patients, the bronchodilators were prescribed within the first 3 days of mechanical ventilation. Sixty-five of those 74 patients received both albuterol and ipratropium bromide. The bronchodilators were typically administered with 4 inhalations every 4–6 hours while on the ventilator. The median duration of therapy was 4 days (interquartile range 1.5–10 d).

Baseline Characteristics

Baseline characteristics (including age, sex, Acute Physiology and Chronic Health Evaluation II score, and race) were similar between the 2 groups (Table 1). However, the patients who received bronchodilators had a greater severity of hypoxemia and a lower ratio of P_{aO_2} to fraction of inspired oxygen than those not prescribed bronchodilators (188 mm Hg versus 238 mm Hg, $p = 0.004$). Furthermore, the subjects prescribed bronchodilators were more likely to have pneumonia during their ICU admission (53% vs 33%, $p = 0.007$).

Outcomes

The patients who received bronchodilators were not more tachycardic (Table 2). There were no significant differences in the incidence of tachyarrhythmias or the amount of potassium replacement, after adjustment for duration of mechanical ventilation. The median duration of mechanical ventilation for the entire study population was 4 days (interquartile range 2–10 d) The median duration of mechanical ventilation for patients prescribed bronchodilators was 8 days (interquartile range 4–14 d), whereas the median for those not prescribed bronchodilators was 3 days (interquartile range 2–8 d) There was no difference in mortality, clinically probable ventilator-associated pneumonia, or incidence of tracheostomy between the 2 groups.

Cost

Administration of inhaled bronchodilators was associated with a total extra cost per patient of $449.35. There was a cost difference between the 2 institutions, due to differences in drug acquisition and administration costs (Table 3).

Discussion

A significant proportion of mechanically ventilated patients at these 2 institutions received inhaled bronchodilators without clear indication. Clinicians preferentially prescribed bronchodilators to more hypoxemic patients, who ultimately required a longer duration of mechanical ventilation. They also preferentially prescribed bronchodilators to patients with pneumonia and more severe hypoxemia. Patients who required longer mechanical ventilation were more likely to be prescribed bronchodilators, which might be explained by fact that patients who underwent longer duration of mechanical ventilation therefore had more days of opportunity to be prescribed bronchodilators. Administration of bronchodilators was associated with only modest cost per patient and no increase in development of tachyarrhythmia.

There are several theoretical benefits of inhaled albuterol in mechanically ventilated patients. Inhaled β agonists enhance mucociliary clearance in normal subjects.[2] Some studies have suggested that mucociliary clearance is profoundly diminished in patients who require mechanical ventilation.[19–21] Konrad et al[19,20] found an association between depressed mucociliary clearance and later develop-

Table 1. Study Population

	Did Not Receive Bronchodilators (n = 132)	Received Bronchodilators (n = 74)	p
Age (mean ± SD)	59.4 ± 17.8	58.4 ± 17.2	0.72
Sex			
Male (n and %)	71 (54)	43 (58)	
Female (n and %)	61 (46)	31 (42)	0.55
Race			
White (n and %)	70 (53)	41 (55)	
Black (n and %)	40 (30)	16 (22)	0.31
Other (n and %)	22 (17)	17 (23)	
APACHE II score (mean ± SD)	26.0 ± 8.1	24.5 ± 7.6	0.22
Day-1 P_{aO_2}/F_{IO_2} (mean ± SD)	238.0 ± 123.2	187.9 ± 91.0	0.004
Pneumonia* (n and %)	44 (33)	39 (53)	0.007
ARDS (n and %)	18 (14)	15 (20)	0.21
ICU admission diagnosis (n and %)			
Sepsis	36 (27)	17 (23)	0.50
Pneumonia	14 (11)	19 (26)	0.005
Pulmonary edema	9 (7)	1 (1)	0.10
ARDS	2 (1.5)	3 (4)	0.35
Other respiratory diagnosis	10 (8)	11 (15)	0.15
Neurologic disease	22 (17)	7 (9)	0.21
Shock nonseptic	14 (11)	7 (10)	1.00
Liver disease	8 (6)	3 (4)	0.75
Pancreatitis	1 (1)	1 (1)	1.00
Gastrointestinal bleeding	13 (10)	2 (3)	0.091
Post-operative	1 (1)	2 (3)	0.30
Other diagnosis	2 (1.5)	1 (1)	1.00

*Pneumonia diagnosed at any time during intensive-care course
F_{IO_2} = fraction of inspired oxygen
APACHE = Acute Physiology and Chronic Health Evaluation
ARDS = acute respiratory distress syndrome
ICU = intensive care unit

Table 2. Outcomes

	Did Not Receive Bronchodilators (n = 132)	Received Bronchodilators (n = 74)	p
Potassium replacement (median and IQR mEq/d)	6 (0–27)	4 (0–17)	0.27
Hours per day of tachycardia (pulse > 110 beats/min) (mean ± SD)	1.0 (0–4.6)	1.6 (0–5)	0.68
Ventilator-associated pneumonia (n and %)	9 (7)	11 (15)	0.08
New-onset tachyarrhythmia (n and %)	20 (15)	16 (22)	0.25
Atrial fibrillation (n)	17	12	0.54
Supraventricular tachycardia (n)	3	5	0.14
Ventricular tachyardia (n)	2	0	
Failed extubation (n and %)	12 (9)	12 (16)	0.13
Tacheostomy (n and %)	15 (11)	14 (19)	0.14
Ventilator days (median and IQR)	3.0 (1.8–7.7)	7.7 (3.6–14.3)	< 0.001
Survivors only (median and IQR)	2.4 (1.7–5.0)	6.1 (3.1–15.7)	< 0.001
Died during hospitalization (n and %)	69 (52)	39 (53)	0.95

IQR = interquartile range

ment of respiratory complications. However, the typical dose of inhaled β agonist required to increase mucociliary clearance is substantially larger than the dose routinely used for bronchodilation.[2]

Table 3. Cost

	Cost Per Patient ($)	
	Center 1	Center 2
Albuterol	206.51	240.19
Ipratropium bromide	192.27	242.49
Total extra cost per patient	398.78	484.68

β agonists also improve respiratory mechanics in patients with ARDS. Wright and Bernard found that airflow resistance was markedly increased (averaging 6 times normal) in patients with ARDS.[22] A follow-up study found that inhaled β agonists significantly decreased airway resistance, peak pressure, and plateau pressure in these patients.[3] Morina et al suggested that intrinsic positive end-expiratory pressure is also decreased by inhaled β agonists.[5] Clinicians may prescribe β agonists on the reasoning that even modestly lowering airway resistance may decrease work of breathing in marginal patients. In patients undergoing spontaneous breathing trials, Mancebo et al,[6] found that albuterol significantly decreased the work of breathing (measured via esophageal manometry), from 9.35 J/min to 8.33 J/min.

Finally, there is accruing evidence that β agonists promote alveolar fluid clearance in lung injury and hydrostatic pulmonary edema models.[7] McAuley et al found that clinically achievable concentrations of albuterol can increase alveolar fluid clearance.[8] And Perkins et al recently presented data from a randomized controlled trial that found a significant decrease in extravascular lung water in ARDS patients who received intravenous albuterol, versus placebo.[23]

Conclusions

Thirty-six percent of the patients mechanically ventilated for $\geq$ 24 hours received bronchodilator therapy without clear indication. Although the cost per patient was fairly modest ($449 per patient), the additional cost to each hospital over one year is about $66,000. A well-designed randomized placebo-controlled trial to study the impact of bronchodilators on clinical outcomes in these patients should be undertaken.

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