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The role of intrinsic efficacy in determining response to a β_2-agonist in acute severe asthma ☆

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Summary
Background: Current guidelines recommend repeated doses of albuterol for the emergency treatment of acute asthma. However, approximately one-third of patients show little or no initial response to this partial β_2-agonist.
Methods: We conducted a randomized, double-blind, proof-of-concept study to investigate whether a *full* β_2-agonist, isoproterenol, offers a therapeutic advantage in adults presenting with acute severe asthma ($FEV_1 < 50\%$) who fail to respond to an initial treatment of the *partial* β_2-agonist, albuterol. Study subjects were randomized to receive a 2-h continuous nebulization of either albuterol (7.5 mg/h) ($n = 10$, mean $FEV_1 = 37\%$ predicted) or isoproterenol (7.5 mg/h) ($n = 9$, mean $FEV_1 = 33\%$ predicted). Respiratory symptoms, vital signs and pulmonary function measures were collected.
Results: Subjects from both treatment groups had similar baseline characteristics. The percent improvements from baseline FEV_1 at 60 and 120 min were significantly higher in subjects receiving isoproterenol than those receiving albuterol (44 vs. 17% and 63 vs. 24%, respectively, $P < 0.05$). The change in symptoms measured by the modified Borg score was also significantly greater in subjects receiving isoproterenol ($P < 0.01$). Both treatments were well tolerated, though the mean increase in pulse rate at 60 and 120 min (21 vs. 1 and 23 vs. 6 beats/min, respectively, $P < 0.05$) and the mean change in serum potassium at

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120 min (−0.52 vs. −0.07 meq/L, $P<0.05$) from baseline were significantly greater in the isoproterenol group.
Conclusions: Our data suggest that in subjects presenting with acute severe asthma who fail to show an initial response to albuterol, the use of a β_2-agonist of higher intrinsic efficacy can be more effective in improving lung function and symptoms.

Introduction

Asthma is a common chronic inflammatory disease of the airways with significant morbidity and mortality.[1,2] Considerable progress has been made in understanding the pathogenesis of asthma and improving its treatment. Despite improvements in the outpatient care of asthma, the emergency treatment of acute asthma remains inadequate.[3,4] Among the 2 million patients presenting to US hospital emergency departments (ED) with acute exacerbations every year, approximately one-third fail to show sufficient improvement to allow safe discharge, and instead require admission to the hospital and sometimes to the intensive care unit.[1–6]

Prompt management of acute asthma is essential to prevent complications.[3,4] Managing patients with acute asthma involves assessing the severity of exacerbation, implementing measures to rapidly reverse airflow limitation, and instituting therapies such as systemic corticosteroids to limit the progression of airway inflammation.[7] β_2-Adrenergic agonists are the most powerful bronchodilators known, and their use is a mainstay of the initial treatment of acute exacerbation of asthma.[7] Despite more than a century of drug development and the current availability of numerous β_2-agonists of widely differing pharmacologic properties, the optimal use of these agents in the management of asthma is not fully determined.

β_2-agonists are generally classified by their receptor selectivity, duration of action, affinity, potency and intrinsic efficacy.[8–10] Intrinsic efficacy refers to the ability of a drug, independent of tissue conditions, to interact with a receptor to activate its downstream signal transduction pathway. It serves as a measure of the relative agonism of a drug or a hormone—i.e., a *partial* agonist is less effective than a *full* agonist in causing a downstream cellular response once bound to its receptor at equal receptor occupancy. The measurement of intrinsic efficacy has uncovered dramatic differences between drugs used clinically that had not been previously apparent in many studies of comparative efficacy. A simple formula to determine the intrinsic efficacy of a β_2-agonist based on measurements of affinity (dissociation constant, K_D) and potency (EC_{50}) has recently been reviewed.[10] The intrinsic efficacy of the most widely used β_2-agonist for the emergency treatment of acute asthma, albuterol, is only 5% that of epinephrine or isoproterenol, which are considered *full* β_2-agonists.[10–12]

Current asthma guidelines recommend repeated doses of albuterol, as needed, for the initial emergency treatment of acute asthma,[7] but do not recommend stepping up therapy to an agonist of higher intrinsic efficacy in patients who fail to adequately respond to albuterol. We hypothesized that the use of β_2-agonists of high intrinsic efficacy (full agonist) may lead to better outcomes in the emergency treatment of patients with acute severe asthma who fail to show an initial response to a partial agonist. To address this issue, we initiated a randomized, double-blind, proof-of-concept study to compare the full β_2-agonist, isoproterenol, with the partial β_2-agonist, albuterol, in acute severe asthma. The results of this study have previously been reported in part in the form of an abstract.[13]

Methods

Study subjects

Adults (18–50 years old) presenting with acute asthma to Ben Taub General Hospital's ED in Houston during the years 1998–2000, were screened for enrollment. Subjects were required to have a history of physician-diagnosed asthma for at least 6 months, be non-smokers or have past history of smoking <10 pack years, and have an $FEV_1<50\%$ of predicted after one initial therapy with nebulized albuterol (2.5 mg) administered in the ED on arrival. Subjects with significant comorbid conditions, those with other respiratory conditions, pregnant women, and those suffering from a life-threatening exacerbation such as those with impending respiratory failure (severe hypercapnia or hypoxemia), hemodynamic compromise, or those needing ICU admission, intubation or non-invasive ventilation were excluded. The study was approved by Baylor College of Medicine's Institutional Review Board, and all subjects gave written informed consent to participate.

Study design

This was a single center, double-blind, randomized parallel group study. Subjects who met the eligibility criteria were randomized in a double-blind fashion to receive either albuterol sulfate 0.083% solution (7.5 mg/h) (Dey Inc, Napa, CA) or isoproterenol 1:200 solution (7.5 mg/h, Sanofi Winthrop Pharmaceuticals, NY). Randomization was performed locally by the hospital's research pharmacy. The study medications were preservative free and were diluted in 20 mL of saline and administered over 2 h by continuous nebulization using an Airlife Misty Max 10™ nebulizer. All study subjects received prednisone 60 mg orally upon randomization and continuous oxygen 3 L/min by nasal cannula.

Efficacy measures

Serial peak flow meter (PEFR) measurements were performed using a Wright peak flow meter every 30 min, and

spirometric measurements at 0, 60, and 120 min. Spirometry was performed and interpreted in accordance with the reproducibility and acceptability criteria of the American Thoracic Society[14] using a Puritan Benett model PB-100 portable spirometer. Peak flow and lung function measurements were performed by the same person throughout the study visit. The severity of dyspnea was assessed every 15 min using the modified Borg score (0–10) with 0 being asymptomatic, 10 being very severe symptoms.[15] The primary endpoint of the study was the mean percent change in FEV_1 from baseline at 60 min following the administration of study medications. Other efficacy measures included the mean percent change in FEV_1 from baseline at 120 min, percent of subjects who achieved a 20% improvement in baseline FEV_1 at 60 min, mean percent change in PEFR from baseline at 60 and 120 min, mean change in modified Borg scores, and disposition status from the ED.

Safety measures

Study subjects were continuously monitored in a dedicated research area and vital signs were monitored every 15 min. All subjects had continuous electrocardiographic and pulse oximetry monitoring. A 12-lead EKG was performed and serum potassium (K^+) was measured at the beginning and the end of the study (0 and 120 min). A subject was withdrawn from the study if he/she experienced significant worsening of symptoms, tachycardia >160 beats/min or any tachyarrhythmias. Subjects withdrawn, were followed and their last evaluable data were included in the analysis under intent-to-treat. At the end of the 2 h of monitoring, study subjects were managed by the ED physician but were followed by study personnel until a disposition decision was made.

Statistical analysis

We initially planned the study to enroll 50 subjects in each arm based on a power analysis that was based on an estimated 30% difference in percent improvement in FEV_1 between the two treatment groups with 0.95 confidence and power of 0.8. Our plan was aborted by the fact that isoproterenol inhalation solution was discontinued from the US market during the conduct of the study. Baseline characteristics of the two treatment groups were compared using Student's *t*-test for continuous variables and the χ^2-test for categorical variables. We used an analysis of variance (ANOVA) model to compare changes in the measured efficacy and safety variables from baseline over time in each of the treatment groups, and used an unpaired *t*-test to compare the measured variables at each time point between the two treatment groups. When the primary assumption of equal variance between the two treatment groups did not hold, we used the Wilcoxon rank-sum test to compare between groups. Change in the Borg score over time was evaluated by repeated-measures mixed-model analysis of variance (SAS version 8.2), with main effects of time and treatment, as well as the first-order interaction. Significance was imparted at the $P<0.05$ level.

Results

Study subjects

A total of 56 subjects were screened for enrollment, and 19 met the inclusion criteria and were randomized to receive study medications. The major reason for exclusion from the study was failure to meet the spirometry criteria ($FEV_1<50\%$). Ten subjects (5 African-American, 4 Hispanic, 1 Caucasian) were randomized to albuterol and 9 subjects (8 African-American, 1 Hispanic) to isoproterenol. Baseline characteristics were similar in both treatment groups except for some difference in the ethnic mix of the subjects as noted above. Of note is the underutilization of maintenance inhaled corticosteroids in both groups as well as the frequent ED visits for asthma in the preceding year which are common findings in inner city asthma patients in the US.

Physiologic response

Mean percent improvements from baseline FEV_1 at 60 min (44% vs. 17%) and 120 min (63% vs. 24%) were significantly higher in subjects receiving isoproterenol than in those receiving albuterol ($P<0.05$) (Fig. 1). Improvements in PEFR were also higher at all time points measured in the group receiving isoproterenol, but these changes did not reach statistical significance (Table 2). Six of the nine subjects receiving isoproterenol (66%) vs. 4 of the 10 subjects receiving albuterol (40%) had a change in $FEV_1>20\%$ in the first hour, while 3 patients receiving albuterol (30%) had a decline in their FEV_1 from baseline in the first hour compared to none of the subjects receiving isoproterenol. Similar superiority of response with isoproterenol was noted during the second hour of treatment.

Symptomatic response

Although the mean Borg score was higher in the isoproterenol group than in the albuterol group at baseline (Table 1),

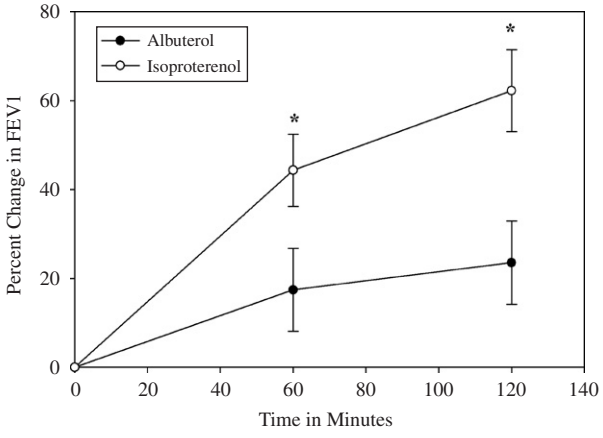

Figure 1 Effect of continuous nebulization of isoproterenol and albuterol on the mean (SE) percent change in FEV_1 at 60 and 120 min compared to baseline. At each time point isoproterenol resulted in a significantly higher improvement in FEV_1 compared to albuterol. SE = standard error, $^*P<0.05$.

Table 1 Baseline characteristics of study subjects.

	Isoproterenol ($n = 9$)	Albuterol ($n = 10$)
Men (n)	5	3
Age in years, mean, (range)	27.6 (18–41)	31.1 (20–47)
Age at asthma diagnosis, years (SD)	12.3 (8.8)	11.8 (14.2)
Hospitalization in past year (n)	3	3
ED visit in past year (n)	6	6
Past smoker (n)	3	2
SABA use (n)	9	10
LABA use (n)	1	1
ICS use (n)	3	2
SaO_2 , mean (range)	94.7 (91–98)	95.9 (93–99)
Modified Borg score, mean (range)	5.5 (3–10)	3.8 (1–7)
Pulse rate (beats/min), mean (range)	104 (83–132)	106.8 (79–130)
PEFR (L/min), mean, (SD)	157.2 (43.8)	148.5 (52.1)
FEV_1 (L), mean (SD)	1.06 (0.33)	1.14 (0.37)
% Predicted FEV_1, mean (range)	33.3 (23–46)	37 (18–48)
Serum K^+ (meq/L), mean (SD)	4.1 (0.32)	3.6 (0.44)*
QTc interval (ms), mean (SD)	409 (37)	427 (35)

*$P<0.05$, albuterol vs. isoproterenol, SABA = short-acting beta-agonists, LABA = long-acting beta-agonists, ICS = inhaled, corticosteroids, SD = standard deviation.

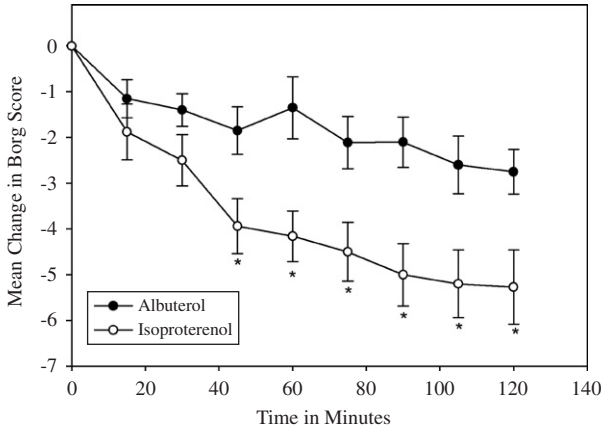

Figure 2 Effect of continuous nebulization of isoproterenol and albuterol on mean change in modified Borg score (SE) from baseline t 60 and 120 min. At all time point after 45 min, isoproterenol resulted in a significantly larger symptom reduction compared to albuterol. SE = standard error, *$P<0.05$.

however, it dropped rapidly with therapy, crossing the albuterol group at 45 min, and remaining well below at all time points until the end of observation at 120 min. Mean scores at 45, 60, 75, 90,105 and 120 min were statistically lower in the isoproterenol-treated subjects compared to those treated with albuterol (Fig. 2) ($P<0.05$). Time effect was highly significant ($P<0.0001$) and time × treatment interaction was also significant at $P<0.05$ (Table 2).

Safety parameters

Safety parameters measured at 60 and 120 min during the study are outlined in Table 3. The mean change in heart rate from baseline was significantly higher at 60 and 120 min in the isoproterenol group compared to the albuterol group (21 vs. 1 and 23 vs. 6 beats/min, respectively, $P<0.05$). More subjects receiving isoproterenol had tachycardia (>100 beats/min) than those receiving albuterol. Only one subject receiving isoproterenol was discontinued from the study for safety purposes because of a heart rate >160 beats/min. The mean decrease in serum K^+ at 120 min from baseline was also significantly greater in the isoproterenol group compared to the albuterol group (−0.52 vs. −0.07 meq/L, $P<0.05$). There were no significant changes between the two groups in systolic and diastolic blood pressure, oxygen saturation measured by pulse oximetry, and QTc measurements over the 2 h of the study.

Disposition from the ED

All patients except one (mentioned above) completed the 120 min study. Four patients in the albuterol group vs. two in the isoproterenol group were admitted to the hospital. The decision to admit the patient to the hospital was made by the ED physician and was based on the overall status of the patient after completion of the study.

Discussion

In this proof-of-concept study we demonstrated that in subjects presenting to the ED with acute severe asthma who fail to show an initial response to a β_2-agonist of low intrinsic efficacy (the *partial* agonist, albuterol), a β_2-agonist of high intrinsic efficacy (the *full* agonist, isoproterenol), was more effective in improving lung function and symptoms. However, although both treatments were well tolerated by the study subjects, the use of an agonist of high

Table 2 Change in measures of lung function and symptoms from baseline at 60 and 120 min.

	Isoproterenol ($n = 9$)	Albutertol ($n = 10$)	P-value
Δ at 60 min			
% Δ in FEV_1 (SE),	44 (8)	17 (9)	0.046
% Δ in PEFR (SE)	48 (11)	30 (11)	0.27
Δ in modified Borg score (SE)	−4 (0.5)	−1 (0.7)	0.04
Δ at 120 min			
% Δ in FEV_1 (SE)	63 (9)	24 (9)	0.01
% Δ in PEFR (SE)	67 (13)	41 (9)	0.12
Δ in modified Borg score (SE)	−5 (0.8)	−3 (0.5)	0.02

Data values are mean (SE), SE = standard error, PEFR = peak expiratory flow rate, FEV_1 = forced expiratory volume in first second.

Table 3 Safety parameters measured at 60 and 120 min.

	Isoproterenol ($n = 9$)	Albuterol ($n = 10$)
60 min		
Heart rate (beats/min)	125 (5)*	109 (4)
Heart rate <100/min (n)	0	3
Heart rate 100–120/min(n)	2	5
Heart rate 120–140/min (n)	6	2
Heart rate 140–160/min (n)	1	0
Systolic BP (mmHg)	130 (6)	130 (6)
Diastolic BP (mmHg)	79 (5)	77 (4)
SaO_2%	94 (3)	95 (2)
120 min		
Heart rate	127 (6)	115 (7)
Heart rate <100/min (n)	0	3
Heart rate 100–120/min (n)	4	4
Heart rate 120–140/min (n)	4	2
Heart rate 140–160/min (n)	1	1
Systolic BP (mmHg)	138 (6)	127 (4)
Diastolic BP (mmHg)	80 (4)	73 (4)
SaO_2%	93 (2)	94 (2)
QTc (ms) (range)	420 (352–484)	418 (340–472)
Serum K^+ (meq/L) (range)	3.6 (3.1–3.9)	3.5 (2.7–4.4)

Data values are mean (SE) except when mentioned otherwise, SE = standard error, SaO_2% = percent oxygen saturation measured by pulse oximetry. K^+ = potassium.
*$P<0.05$.

intrinsic efficacy may be associated with an increased incidence of adverse effects such as hypokalemia and tachycardia due to activation of β_2-receptors in non-target sites.

Historically, isoproterenol, a non-selective β-agonist of high intrinsic efficacy was the first agent to be widely used via nebulization.[8,16] Albuterol was introduced in the US in 1984. Like isoproterenol, it has a rapid onset of action but unlike isoproterenol, it is more than 1000 fold functionally selective for the β_2 -receptor subtype over the β_1 subtype.[9] Because of its excellent safety profile and quick onset of action, albuterol delivered either by nebulization or inhaler devices has largely replaced the non-selective β-agonists, isoproterenol and epinephrine, in the treatment of acute asthma exacerbations.[17] Even though albuterol is a *partial* agonist, clinical data indicate that it is effective in relieving acute bronchospasm in most patients with mild-to-moderate asthma exacerbation, and may be as effective as subcutaneous epinephrine in this situation.[18] This paradox, that two drugs with markedly different intrinsic efficacies can nonetheless have similar clinical efficacies, can be explained by understanding the effects of receptor numbers and functional antagonism on cellular responses. Airway smooth muscle cells, which express high levels of β_2-adrenergic receptors, have more receptors than are necessary to fully activate downstream responses in normal situations (''spare receptors''). Thus, even though albuterol has a low intrinsic efficacy, it is able to elicit a comparable downstream

response under conditions of low receptor desensitization and low functional antagonism such as the case in mild asthma exacerbations.[10] However, clinical studies indicate that up to one-third of patients with acute severe exacerbation have poor or no initial response to therapy and may require prolonged and aggressive therapy, hospital admission, intubation and mechanical ventilation.[5,6] In such situations, β_2-adrenoceptors may be functionally antagonized by inflammatory mediators and there may be fewer "spare' receptors due to desensitization from the use of multiple doses of rescue β_2-agonist at home.[19–21] The submaximal efficacy of a *partial* agonist such as albuterol may only become apparent in this setting, and a *full* agonist may have a therapeutic advantage (Fig. 3).[10]

Despite this potential therapeutic advantage for using high intrinsic efficacy β_2-agonists in certain asthma settings, only few studies have addressed the clinical utility of such agents in severe asthma exacerbation. In a multicenter, randomized, double-blind, placebo-controlled study, patients with acute asthma receiving inhaled fenoterol (an agonist with high intrinsic efficacy) had significantly more improvement in airflow than those receiving inhaled albuterol.[22] In another small study from Japan, children suffering from acute severe asthma not responding to conventional therapy were successfully treated with continuous nebulization of isoproterenol.[23] A more recent study demonstrated superiority of formoterol, a β_2-agonist of relatively high intrinsic efficacy (~40% that of isoproterenol[10]) over albuterol in acute severe asthma.[24] Our study is in agreement with these studies as it demonstrates an advantage of using a β_2-agonist of high intrinsic efficacy in a situation when airway obstruction is severe despite the use of a β_2-agonist of low intrinsic efficacy, such as albuterol.

However, the administration of high intrinsic efficacy β_2-agonists cannot be routinely justified for every patient with acute asthma because they can potentially activate receptors in non-target sites such as the heart and skeletal muscles and their use in high doses may be associated with an increased incidence of adverse effects. This was clearly demonstrated in the study comparing fenoterol with albuterol in the acute setting described above[22] as well as in our study although the increase in heart rate observed with isoproterenol in our study may also be secondary to activation of cardiac β1 receptors. The risk–benefit ratio in specific settings will need to be further defined in future clinical trials. In addition, in vitro studies indicate that β_2-agonists with high intrinsic efficacy may induce more receptor desensitization than those with low intrinsic efficacy.[10] This fact is also supported by some in vivo studies[25,26] but not by others.[27] For example, desensitization to the bronchodilator effects of formoterol, a long-acting β_2-agonist of relatively high intrinsic efficacy, has been observed with its regular use in some studies,[25] whereas it has not been shown with the regular use of salmeterol, a long-acting β_2-agonist of very low intrinsic efficacy.[26]

Our study has certain limitations. We enrolled a small number of subjects in this study because of the discontinuation of the study medication, isoproterenol solution, from the US market during the study. Our findings need to be confirmed in additional trials using other β_2-agonists of high intrinisic efficacy to be certain that the superior clinical

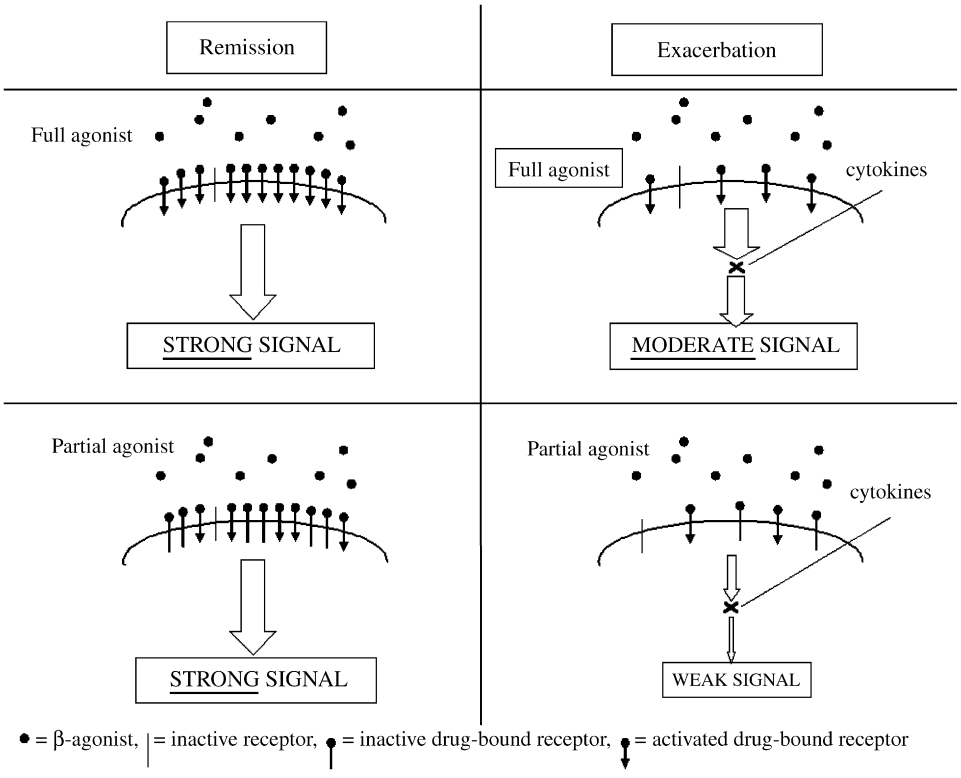

Figure 3 Schematic representation for the potential differential effects between full and partial beta-agonists on airway smooth muscle during remission and during an acute severe exacerbation of asthma; note that the line indicating functional antagonism by cytokines results in attenuation of beta-agonist signalling.

efficacy reflects the higher intrinsic efficacy rather than some other pharmacologic properties of isoproterenol. For safety purposes, we were only able to screen and enroll subjects who had already received an initial dose of albuterol and therefore could not evaluate the initial response to both agonists upon arrival in the ED. However, we believe that our study population represents the one which may benefit from treatment with a full agonist as opposed to a partial agonist. We used similar doses for both albuterol and isoproterenol despite the fact that these agonists have different potencies (isoproterenol > albuterol). However, in a previous study on a similar patient population with acute asthma, there was no documented advantage from administering albuterol in a higher dose than what we used (7.5 mg/h[28]). Thus, we believe that the difference in potency in this situation did not influence our findings. Several other factors which include the pre-hospital use of asthma medications such as inhaled corticosteroids or β_2-agonists and genetic factors such as β-receptor polymorphisms, may have influenced the bronchodilator response in our subjects. While these confounders are corrected for by the similar baseline characteristics in both treatment groups, the ethnic mix of our patient population was not identical as we had slightly more African-American patients in the isoproterenol group. Future studies need to perform genetic analyses to determine whether receptor genotype or haplotype may influence the response to β-agonists of different intrinsic efficacy in acute asthma.

In conclusion, our study results suggest that in subjects presenting to the ED with acute severe asthma who fail to show an initial response to a β_2-agonist of low intrinsic efficacy, a β_2-agonist of high intrinsic efficacy can be more effective in improving lung function and symptoms. This pharmacologic characteristic needs to be considered in future studies and in the development of new β_2-agonists for the treatment of acute asthma.

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Disclaimer: The authors do not have any competing interests in relation to this study.

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