Original Article

Nonprescription Racemic Epinephrine for Asthma

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What is already known about this topic? There is little information on the relative efficacy of racepinephrine and albuterol for patients with asthma.

What does this article add to our knowledge? It indicates that nebulized racepinephrine has less bronchoprotective effect than albuterol.

How does this study impact current management guidelines? Racepinephrine should not be used in place of albuterol to treat acute asthma.

BACKGROUND: Inhaled racepinephrine (RE) (Asthmanefrin) became available in September 2012 as a nonprescription treatment for bronchospasm based on a 1986 US Food and Drug Administration rule. It contains 11.25 mg RE in 0.5 mL and is delivered by a handheld electronic nebulizer. In 2001, we conducted a pilot study that was never published. Now that the product is promoted as a replacement for epinephrine chlorofluorocarbon metered-dose inhaler (Primatene), we provide the results of that study. Methacholine challenge was used as a bioassay.

OBJECTIVE: To determine the dose of RE that is equivalent to nebulized albuterol.

METHODS: Four subjects, 18 to 45 years old, with mild stable asthma completed the pilot study. Methacholine challenge was performed on the first screening day, without pretreatment, and then on different days, 15 minutes after 1.25 mg albuterol and 2.5, 5, 10, and 20 mg RE delivered by a Pari LC Plus nebulizer. The end point was the provocative concentration of methacholine that caused a 20% decrease in FEV_1. Data were log transformed and analyzed by an ANOVA for repeated measures.

RESULTS: There was a significant dose response for RE. The geometric mean provocative concentration of methacholine that caused a 20% decrease in FEV_1 was 44 mg/mL (95% CI, 23-85 mg/mL) after albuterol, and 10.2 mg/mL (95% CI, 3.5-30 mg/mL) after the 10-mg dose of RE (approximate nonprescription dose) ($P = .001$). There were no adverse effects.

CONCLUSION: RE provides less bronchoprotection from methacholine than does albuterol and may be less effective in treating acute bronchospasm. © **2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;■:■-■)**

Key words: *Nonprescription; Racepinephrine; Albuterol; Methacholine challenge; Bronchoprotection*

Racepinephrine hydrochloride inhalation solution, United States Pharmacopeia 2.25% (RE), formerly called racemic epinephrine, has been used for decades for the treatment of croup,[1] bronchiolitis,[2] and postextubation stridor.[3] In September 2012, it became available as a nonprescription treatment for acute asthma under the brand name of Asthmanefrin (Nephron Pharmaceuticals Corp, Orlando, Fla) (Figure 1). Each 0.5-mL unit dose sterile vial contains 11.25 mg of RE base (equivalent to 5.6 mg of L-epinephrine) and is delivered by a handheld electronic ultrasonic nebulizer using a vibrating mesh technology (EZ Breath Atomizer, Health & Life Co Ltd, New Taipei City, Taiwan).

In 1986, the US Food and Drug Administration (FDA) issued a Final Rule that stated that RE, delivered by handheld bulb atomizer, was recognized as safe and effective for nonprescription treatment of asthma.[4] However, a nonprescription product only became available in the United States after Primatene Mist MDI (L-epinephrine) (Armstrong Pharmaceuticals, Inc., Rancho Cucamonga, CA) was withdrawn because it contained a chlorofluorocarbon propellant. Asthmanefrin is promoted as an alternative to Primatene Mist (Figure 1). A meta-analysis of 6 randomized trials that compared inhaled epinephrine to β_2-agonists in the treatment of acute asthma in the emergency department indicated that $\leq$2 mg per dose of L-epinephrine was less effective than 2.5 or 5 mg of albuterol per dose, but >2 mg

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Abbreviations used
FDA- US Food and Drug Administration
PC_{20}- Provocative concentration of methacholine producing a 20% decrease in FEV_1
RE- Racepinephrine (formerly referred to as racemic epinephrine)

per dose produced effects similar to 5 mg of albuterol per dose.[5] Only one of these studies used RE, and it did not include an objective measurement of airway function, only a pulmonary index score.[6] Thus, there is little information on the relative efficacy of RE and albuterol.

In 2001, Nephron Pharmaceuticals funded a pilot study at the University of Florida to determine the relative efficacy of RE and nebulized albuterol. Based on the results of that pilot study, the company chose not to conduct a therapeutic equivalence trial. Because Nephron is actively promoting the nonprescription product now, we report here the results of that pilot. We chose to use bronchoprotection as the end point because it is the most sensitive method of detecting differences among β-agonists,[7] dose,[8] or delivery method.[9] The objective of this study was to determine the dose of RE that is equivalent to low-dose (ie, half-strength) albuterol nebulizer solution (1.25 mg) for bronchoprotection.

METHODS

The protocol was approved by the University of Florida Institutional Review Board (no. 84-2001), and all the subjects gave written informed consent. Inclusion criteria were subjects with mild stable asthma, ages 18 to 30 years, nonsmokers for at least 6 months before the study, a smoking history of less than 10 pack years, an $FEV_1 > 65\%$ predicted, a baseline provocative concentration of methacholine that caused a 20% decrease in FEV_1 (PC_{20}) $\leq$4.0 mg/mL when using the 5-breath dosimeter method,[10] normal electrocardiogram, and no history of intolerance to sympathomimetics. The subjects could not be taking antihistamines or anticholinergics, and female subjects could not be pregnant and had to be using an acceptable method of birth control. Exclusion criteria included hypertension, respiratory tract infection in the previous 6 weeks, and oral corticosteroid use; emergency department visit; or hospitalization for asthma in the preceding 3 months.

During the first screening visit, spirometry was performed to determine the baseline FEV_1. Each subject then underwent a methacholine challenge. The subject returned the next day. During the second visit, methacholine challenge was begun 15 minutes after inhaling 1.25 mg of nebulized albuterol in 3 mL saline solution through a Pari LC Plus nebulizer (Pari Respiratory Equipment Inc, Midlothian, Va). A 4-fold increase in PC_{20} was required to select subjects capable of demonstrating a bronchoprotective response to albuterol. At the subsequent visits, on separate days, the subjects underwent methacholine challenge beginning 15 minutes after inhaling 2.5, 5, 10, and 20 mg of RE each in 3 mL saline solution. The study visits were separated by at least 24 hours. Doses of RE were sequentially increased at succeeding visits until the 20-mg dose was reached. The heart rate was measured before each dose and before commencing methacholine challenge.

Statistical analysis

An ANOVA for repeated measures was used to evaluate differences among $\log_2$ PC_{20} values. The Ryan-Emnot-Gabriel-Welsch multiple comparison procedure[11] was used to determine the source of the difference when ANOVA was significant. A P value $<.05$ was considered significant. The RE data were fit to a maximum effect pharmacodynamic model,[12] and the maximum effect and dose of RE producing 50% of the maximum effect were determined.

RESULTS

Five subjects signed the informed consent, and 4 subjects completed all study days. The fifth subject did not have a $PC_{20} \leq 4$ mg/mL at screening. There was a significant dose response for RE; the geometric mean (95% CI) PC_{20} was 0.78 mg/mL (95% CI, 0.35-1.8 mg/mL) for no drug (zero dose on the first screening visit), 3.0 mg/mL (95% CI, 0.11-8.0 mg/mL) for 2.5 mg RE, 4.7 mg/mL (95% CI, 1.4-15 mg/mL) for 5 mg, 10.2 mg/mL (95% CI, 3.5-30 mg/mL) for 10 mg, and 16.4 mg/mL (95% CI, 4.2-63 mg/mL) for 20 mg RE (Figure 2). The maximum effect was 45 mg/mL, and 50% of the maximum effect was 5 mg. The geometric mean (95% CI) for 1.25 mg albuterol, 44 mg/mL (95% CI, 23-85 mg/mL), was significantly higher than all doses of RE, including the highest dose of RE (20 mg) ($P < .05$) (Table I). It was 4.3 times more bronchoprotective than the 10-mg RE dose, which is approximately the approved nonprescription dose (11.25 mg) ($P = .001$) (Table I). There were no clinically relevant adverse effects during the study.

DISCUSSION

The results of this pilot study indicated that RE was much less effective than albuterol in protecting against methacholine-induced bronchospasm and that the effect begins to plateau after 10 mg. It is noteworthy that the difference between the 10-mg dose of RE, which is approximately the nonprescription dose (11.25 mg) and low-dose nebulized albuterol (1.25 mg), was statistically significant with only 4 subjects. Presumably, if a full therapeutic dose of albuterol were given (ie, 2.5-5 mg), then an even greater bronchoprotective effect would have been observed as has been reported for histamine challenge.[9]

In vitro, epinephrine is more effective than albuterol in relaxing airway smooth muscle,[13] but results of randomized clinical studies have been conflicting. Some studies have shown albuterol to be more effective than epinephrine for bronchodilatation,[14-17] whereas others have shown no difference for this end point.[6,13,18-20] Only one of these studies[6] used RE, whereas the remainder studied L-epinephrine. However, it is unlikely that the presence of R-epinephrine in RE would influence the results. Differences among studies in dosing, delivery method, and severity of bronchospasm complicate interpretation of these results. In 1 study, Baldwin et al[13] found nebulized albuterol and epinephrine to have similar bronchodilator effects in subjects with mild asthma, but the bronchoprotective effect of albuterol was much greater than those of epinephrine, as in our study.

Bioassay with methacholine is the most robust way to test for differences in dose, delivery method, or drug on efficacy when the airway muscle is placed under increased load.[7-9] However, a limitation of this method when comparing a catecholamine and β_2-agonist is that it is affected by differences in duration of action of these 2 drug classes. The interaction of epinephrine with the β-receptor is rapidly terminated by re-uptake into nerve terminals and degradation by catechol-O-methyltransferase, whereas the duration of effect of albuterol is not affected by these