Acute Allergic Rhinitis Increases Endogenous Epinephrine Resulting in Increased Heart Rate

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RATIONALE

- The pathophysiology of allergic rhinitis involves allergen-induced mast cell degranulation and subsequent release of allergic mediators, including histamine and cytokines.
- While the localized actions of allergic mediators (vasodilation, increased vascular permeability, and mucus secretion) are well-understood, far less is known about the effects of these allergic mediators on the cardiovascular system.[1]
- We investigated the systemic effect of an acute allergic rhinitis reaction by measuring endogenous epinephrine concentrations and vital signs (blood pressure and heart rate) after allergen challenge.

METHODS

- A series of cross-over pharmacokinetic and pharmacodynamic clinical trials were conducted to evaluate the comparative bioavailability of the novel intranasal epinephrine spray (***neffy***) against epinephrine injection products that were compliant with Good Clinical Practice. Those studies were conducted in winter to avoid allergic season. Two studies included allergic rhinitis patients who underwent nasal allergen challenge (NAC). [2,3] In both studies, endogenous epinephrine levels, blood pressure and heart rate were measured before epinephrine was administered, during normal conditions for three times and once after the induction of allergic rhinitis symptoms.
- Positive allergen challenge was defined as Total Nasal Symptom Score (TNSS) of ≥5 out of 12-and a congestion score of ≥2 out of 3; normal condition was defined as TNSS score of ≤2 out of 12 and a congestion score of ≤1 out of 3.[4]
- Mean values of epinephrine concentration, blood pressure and heart rate were compared between normal condition and rhinitis condition with analyses of variance (ANOVA).

Subjects underwent NAC:

Study #1: 36 subjects with history of seasonal allergic rhinitis were exposed to one of the test tree or grass allergens with the allergen dose determined at screening or a 3-hour OHIO Chamber exposure.[5]

Study #2: 36 subjects with seasonal allergic rhinitis were exposed to cedar pollen in the OHIO Chamber for three hours.

RESULTS

Mean Epinephrine Concentration and Vital Signs (SD) by Condition (Figures 2 and 3)

- Subjects ranged in age from 19 to 55 years in Study 1 and 24 to 55 years in Study 2. In Study 1, mean epinephrine levels under normal nasal conditions ranged from 18.3 to 21.6 pg/mL and increased to 28.7 pg/mL after allergic rhinitis was induced (Figure 2).
- In Study 2, mean epinephrine levels in the normal conditions ranged from 20.0 to 23.5 pg/mL and increased to 34.5 pg/mL after allergic rhinitis was induced (Figures 3).
- Corresponding increases in heart rate were also observed after induction of allergic rhinitis (Figures 2 and 3). There were no significant changes in systolic or diastolic blood pressure.
- In Study 1, the mean heart rate under normal nasal conditions ranged from 66.1 to 67.2 bpm and increased to 69.2 bpm after rhinitis symptoms were induced; the comparison was not statistically significant (p=0.532). By contrast, in Study 2, the mean heart rate under normal nasal conditions ranged from 60.4 to 60.9 bpm and increased after rhinitis symptoms were induced to 63.7 bpm.
- When compared based on the TNSS level, the increase of endogenous epinephrine appears to be minimal following NAC, while the increase appears to be proportional following allergen chamber exposure (Figure 1).

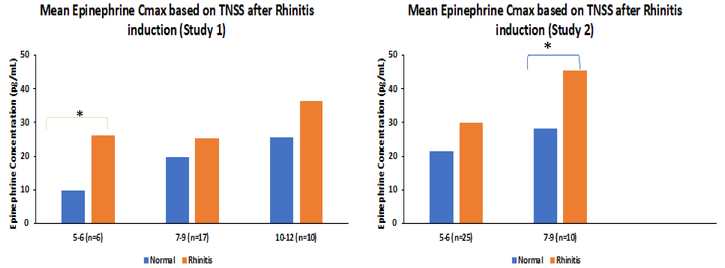
SAFETY RESULTS

The study treatments were well tolerated, with only mild or moderate treatment emergent adverse event (TEAEs) being reported.

CONCLUSIONS

While the vasodilation and vascular permeability associated with allergic rhinitis are most apparent locally, the current findings raise the possibility that even the relatively minor subsequent systemic increases of allergic mediators that occur following induced allergic rhinitis may have systemic effects. A mild systemic vasodilatory response following release of allergic mediators may, in fact, elicit a sub-clinical decrease in blood pressure, causing the release of endogenous epinephrine and a subsequent increase in heart rate, supporting the stabilization of blood pressure as well as relieving allergic symptoms.

Figure 1: Mean Epinephrine C_{max} based on TNSS after Rhinitis Induction



The arm of Normal 3 were used as Normal for Studies 1 and 2 because their mean epinephrine concentrations were median in the study. Comparisons were made between each Normal arm vs rhinitis arm by study.

Acute allergic rhinitis resulted in a small but significant increase in endogenous epinephrine that was accompanied by increased heart rate

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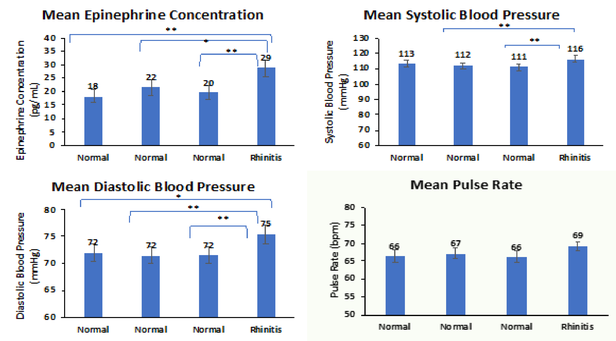
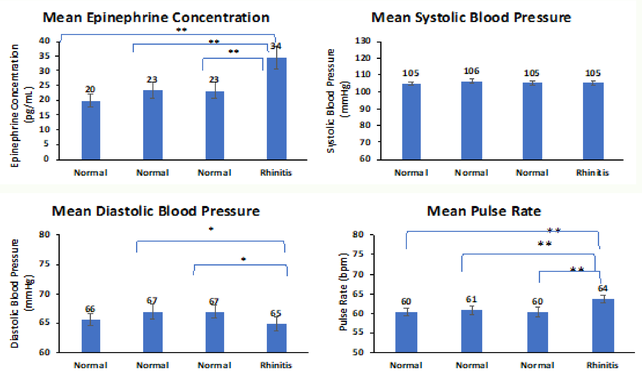
Figure 2: Study 1 (NAC)



*<0.05, **<0.01

Figure 3: Study 2 OHIO Chamber



*<0.05, **<0.01

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