

Time to Symptom Resolution: An Efficacy Endpoint for the Effectiveness of Anaphylaxis Treatments

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Introduction & Rationale

The Problem: The efficacy of epinephrine for treating anaphylaxis has never been studied in a controlled clinical study, making it difficult to compare the advantages of different treatment regimens.

The Solution: Time to resolution of symptoms is proposed as a primary endpoint ethically assessed in a clinical trial. Secondary endpoints can include need for additional IM epinephrine, concomitant medications, incidence of biphasic reactions.

Key Advantage: Provides a measurement of efficacy that is meaningful to both patients and physicians.

Objective: Test the endpoint using a novel inhaled form of epinephrine.

Importance of Early Intervention

Histamine increase begins immediately after exposure to the allergen, usually within 2 minutes.¹

- Correlation between histamine levels at 2 minutes and overall reaction severity¹

Histamine produced for only about 15 minutes after exposure.^{2,3}

Study Design

Study Type: Open-label, single site, investigator led, proof-of-concept study.

Enrollment: Patients visiting the clinic for skin prick tests were consented. Those that developed a systemic allergic reaction (\geq Grade 2 on the WAO Scale⁴) were immediately enrolled and given a novel inhaled epinephrine MDI.

Dosing Protocol: On confirmation of reaction, patients are given one dose (2 inhalations) of a novel form of inhaled epinephrine (0.25 mg epinephrine).

Symptoms are regraded after 2 minutes. If symptoms do not resolve after 2 minutes, a second dose is given. Symptom scoring and dosing is repeated until symptoms resolve, or a maximum of 4 doses (1.0 mg epinephrine) is given. For safety, IM epinephrine is available at the investigator's discretion.

Symptom Resolution: Defined as Grade 1 or lower reaction

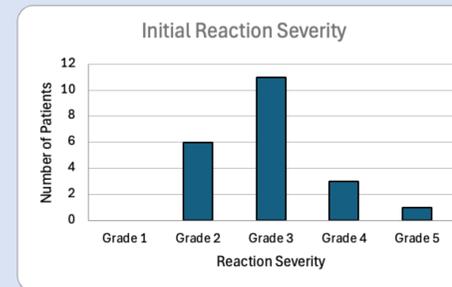
Table 1: Patient demographics

Number of Patients	21
Sex	21 female
Average Age	50 years
Average BMI	30 kg/m ²
Antigen Challenge	Metabisulfite 19, NSAID 2
Baseline Vital Signs	Mean (range)
Systolic Blood Pressure	121 (100 - 139) mm Hg
Diastolic Blood Pressure	74 (61 - 88) mm Hg
Heart Rate	77 (59 - 102) mm Hg
Respiration Rate	12 (12 - 12) mm Hg

Response to Allergen Challenge

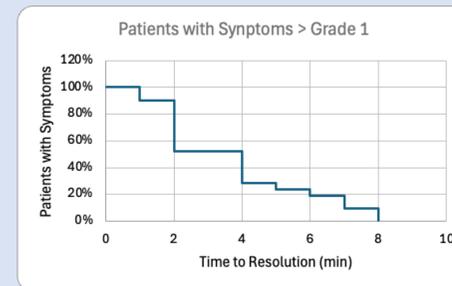
Patients responded to the allergen challenge with moderate to severe reactions: Median reaction was Grade 3 (range Grade 2 to Grade 5).

Figure 1: Severity of the initial reaction



Results

Figure 2: Kaplan-Meier curve for symptom resolution



Patients responded quickly to treatment: median time to symptom resolution was 3.6 minutes.

No correlation between initial reaction severity and time to resolution.

Nearly half of patients resolved directly to Grade 0 (i.e. no symptoms):

- 43% (9 of 21) resolved directly to Grade 0
- 57% (12 of 21) resolved to Grade 1

No patients required all 4 doses:

- 100% of patients resolved with 3 doses or less
- 90% of patients resolved with 2 doses or less
- 48% of patients resolved after the first dose (i.e. time to resolution < 2 minutes)

There were no bi-phasic reactions.

No patients required IM epinephrine, concomitant medications, or emergency treatment.

Safety

No Serious Adverse Events: No SAEs were reported in the study.

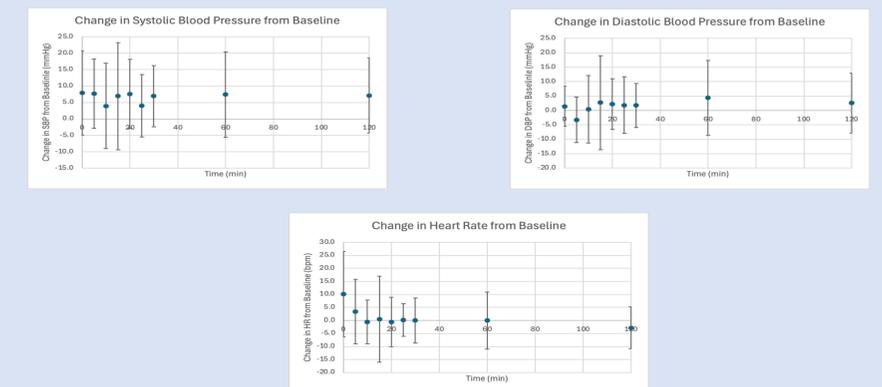
Adverse Events:

- 86% (18 of 21) patients reported tremors/shaking
- Fatigue, headache, anxiety, elevated tryptase reported in no more than 1 patient each
- All AEs were expected and resolved without intervention
- The overall safety profile observed in the GHL-101 study was consistent with the expected pharmacologic effects of epinephrine and comparable to findings reported following administration of approved epinephrine auto-injectors.^{5,6,7}

Pharmacodynamics

- Mean SBP and DBP unchanged throughout study
- Mean heart rate increased approximately 10 bpm immediately after the first 2 inhalations, but returned to baseline by 5 minutes

Figure 3: change in SBP, DBP and HR over the 2-hour observation period



Conclusion

Time to symptom resolution is a practical and ethical endpoint in a controlled clinical setting.

The novel inhaled epinephrine demonstrated **positive efficacy** and a **strong safety profile** in treating anaphylactic reactions.

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