

Epinephrine Plasma Concentration and Hemodynamic Threshold Response Following Sublingual Epinephrine Administration

Matthew Greenhawt MD, MBA, MSc¹; David Golden²; Nils F. Confer PhD³; Elisabeth Kilroy PhD³; Gary Slatko MD³

An analysis of plasma epinephrine exposure and cardiovascular responses in healthy adults

INTRODUCTION

- Non-injectable epinephrine formulations can produce a wide range of plasma epinephrine exposures
- Whether higher systemic epinephrine exposure translate into greater cardiovascular (CV) effects is unclear

OBJECTIVE

Characterize epinephrine exposure-hemodynamic relationships following sublingual epinephrine administration

Background & Objective

BACKGROUND

- Epinephrine is first-line therapy for anaphylaxis
- Plasma epinephrine exposure can be highly variable both between and within subjects
- The relationship between epinephrine exposure and hemodynamic effect are important treatment considerations

OBJECTIVE

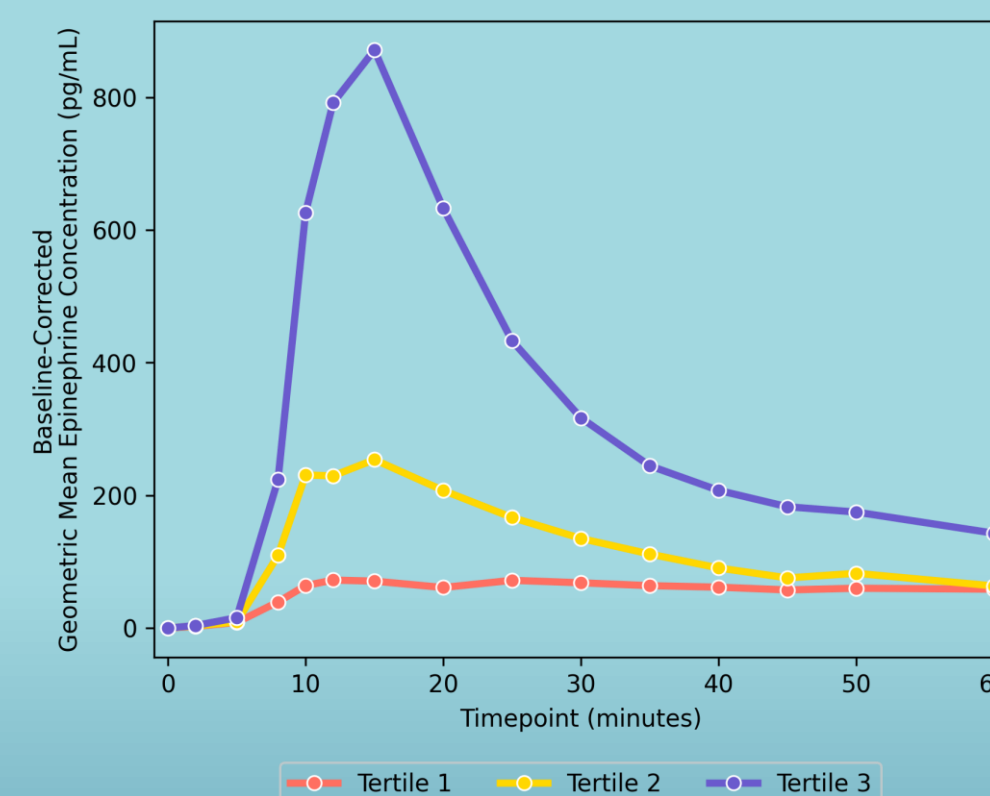
- Evaluate the relationship between plasma epinephrine exposure and CV responses following sublingual epinephrine administration

Study Design

- Pooled analysis of three clinical studies
- Healthy adults (N = 124)
- Single-dose sublingual epinephrine film
- Plasma epinephrine measured over 240-360 minutes
- Heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) assessed concurrently
- Subjects stratified into tertiles based on observed baseline-corrected maximum concentration (C_{max})
- Maximum effect (E_{max}) and time-matched baseline-corrected changes in hemodynamic parameters were evaluated.
- Comparisons across tertiles were performed using one-way ANOVA.
- A quartile analysis demonstrated no material differences from the tertile analysis observations, but reduced the number of observations per group

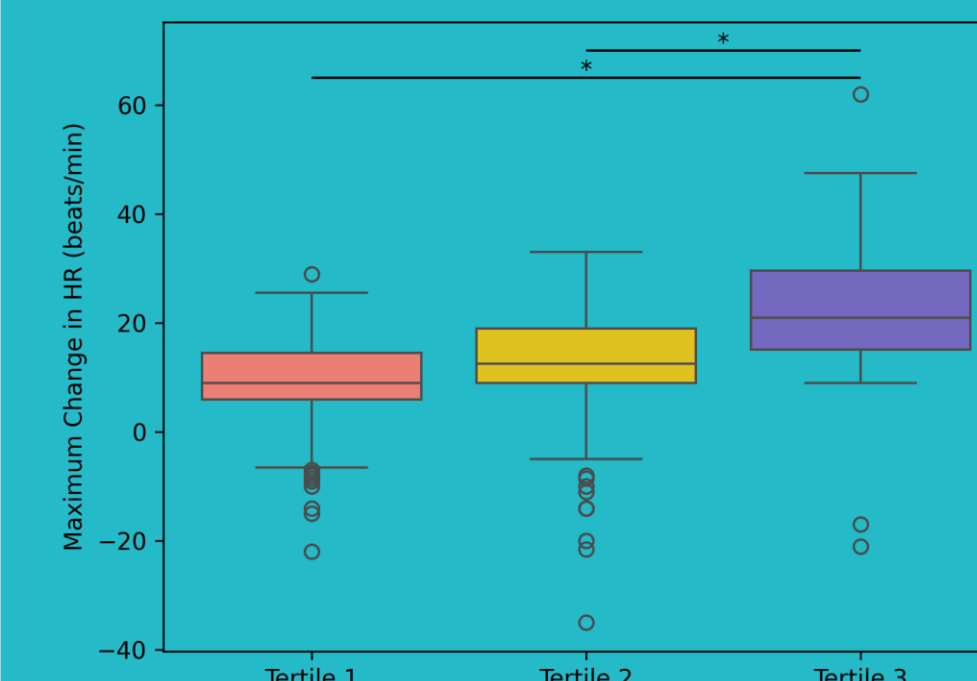
Plasma Epinephrine Exposures

- Broad range of epinephrine C_{max} were observed
- Subjects stratified into tertiles based on baseline-corrected C_{max} values
- Tertile Cutoffs:
 - Tertile 1: <214.6 pg/mL
 - Tertile 2: 214.6–654 pg/mL
 - Tertile 3: >654 pg/mL



Heart Rate Responses

- Maximum HR increases were modest across epinephrine exposure tertiles
- Maximum HR response differed significantly across tertiles, with Tertile 3 demonstrating significantly greater increases compared with either Tertile 1 or Tertile 2.

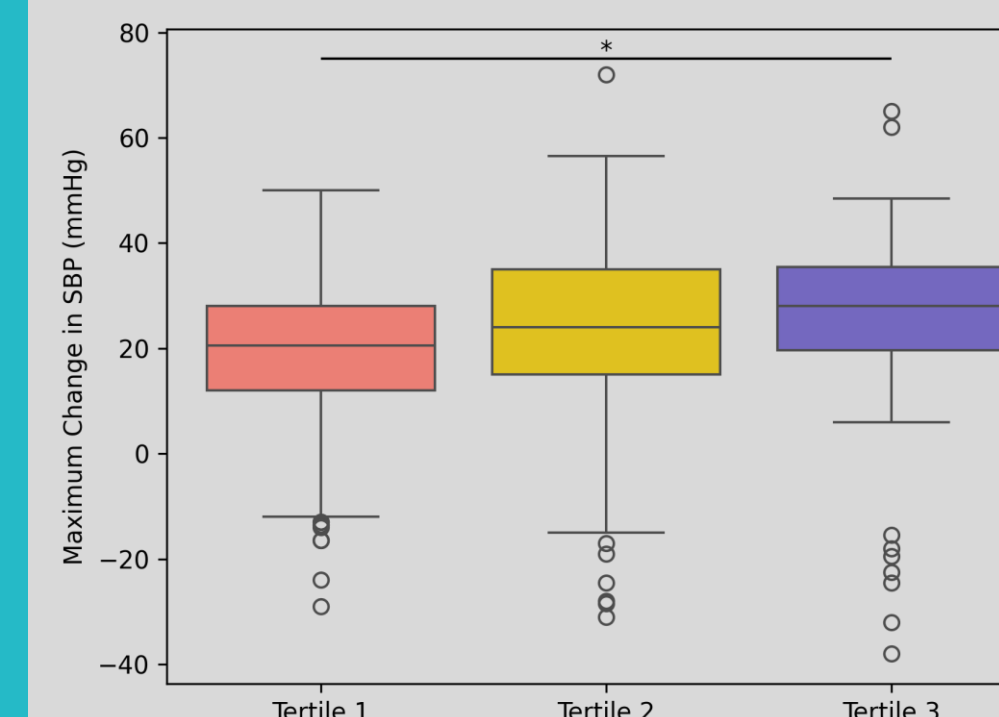


* = p<0.05

- No significant differences in maximum HR were observed between Tertile 1 and middle tertiles Tertile 2

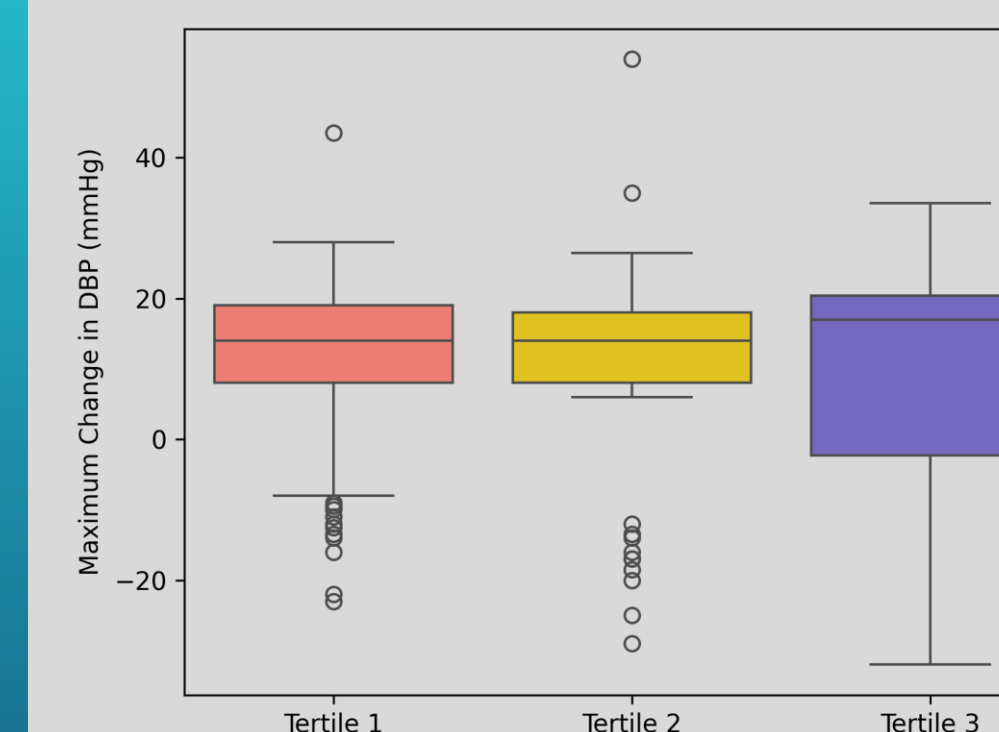
Blood Pressure Responses

- Median change in maximal SBP elevations were statistically different between Tertile 1 and 3
- Higher epinephrine exposure did not lead to clinically meaningful differences in maximal SBP effects



* = p<0.05

- DBP responses plateaued across higher epinephrine tertiles and did not drive greater DBP elevations



Key Messages

- Maximum hemodynamic responses did not consistently demonstrate a linear exposure-response relationship
- Increasing plasma epinephrine exposure beyond mid-range concentrations did not amplify CV effects
- Higher plasma epinephrine exposure did not correlate with proportionally greater hemodynamic effects
- Hemodynamic responses plateaued even in the presence of higher epinephrine exposures
- Findings support the hemodynamic tolerability of sublingual epinephrine delivery

DISCLOSURES:

1. MG is employed by AAFA and has received consultant fees from Aquestive Therapeutics, ARS, DBV, Takeda, Novartis, ALK-Abello, Genentech, and Prota. He is a speaker for ARS and Genentech. He is an unpaid member of the scientific advisory council for National Peanut Board and the medical advisory board of the International Food Protein Induced Enterocolitis Syndrome Association. He serves as a member of the Brighton Collaboration Criteria Vaccine Anaphylaxis 2.0 working group and is the senior associate editor for the Annals of Allergy, Asthma, and Immunology.
2. DG has received consultant fees from Aquestive Therapeutics, ARS, Thermo Fisher, Orexo, Kokua, Novartis, Celldex, and Blueprint.
3. NC, EK, and GS are/were employees at Aquestive Therapeutics.

REFERENCES

AQST109-301 data on file, Aquestive Therapeutics, Inc.

DISCLAIMER

This product candidate has not been approved for use by the FDA. Clinical performance, safety and use have not been established.

ACKNOWLEDGMENTS

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