

Impact of Angioedema on the Pharmacokinetics of Epinephrine Following Administration via Sublingual Film (Anaphylm™)

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INTRODUCTION

- Anaphylm (also known as DESF), a sublingual film that delivers epinephrine, is under development for the treatment of Type 1 allergic reactions, including anaphylaxis.
- Oral angioedema, a potential symptom of Type 1 allergic reactions, is a condition with unknown impact on sublingual absorption.
- To investigate this potential issue, a novel angioedema model was developed. To this end, a pilot study was performed by injecting miniature swine with histamine 10 mg/mL.
- Miniature swine offers a similar sublingual mucosa, but lower enzyme expression. The lower enzyme expression, necessary for the prodrug conversion to epinephrine, allows for a slower PK profile that can be examined for potential changes in absorption under these conditions.
- Results indicate that 3 histamine injections of 20 µL each—2 in the lips and 1 in the tongue—induced reproducible angioedema that is contained in those areas.
- This animal model was subsequently used to investigate the impact of oral angioedema on the pharmacokinetics (PK) of epinephrine delivered via Anaphylm.

METHODS

STUDY DESIGN

- This preclinical, single-center study was performed in 10 male Yucatan miniature swine.
- Each animal received 3 injections of 20 µL each—2 in the lips and 1 in the tongue.
 - Group 1 (n=5) received injections of saline
 - Group 2 (n=5) received injections of histamine (10 mg/mL) reconstituted with saline
- Caliper measurements of lip and tongue thickness were performed at baseline (pre-injections) and at 20 and 40 minutes after the injections.
- Forty (40) minutes after the injections, each animal had Anaphylm 12 mg administered sublingually.
- Epinephrine PK levels were measured baseline (pre-Anaphylm administration) and at 2, 5, 10, 12, 15, 17, 20, 25, 30, 40, 60, 90, 120, 180, 240, 360, and 480 minutes after Anaphylm administration.

RESULTS

ANGIOEDEMA MEASUREMENTS

- In the histamine-treated group, both lip (Figure 1) and tongue (Figure 2) swelling peaked at 20 to 40 minutes post-injection.
 - Range in peak lip thickness: 122% to 155%
 - Range in peak tongue thickness: 119% to 153%
- Swelling was not observed in saline-treated control group

Figure 1: Lip Thickness Over Time

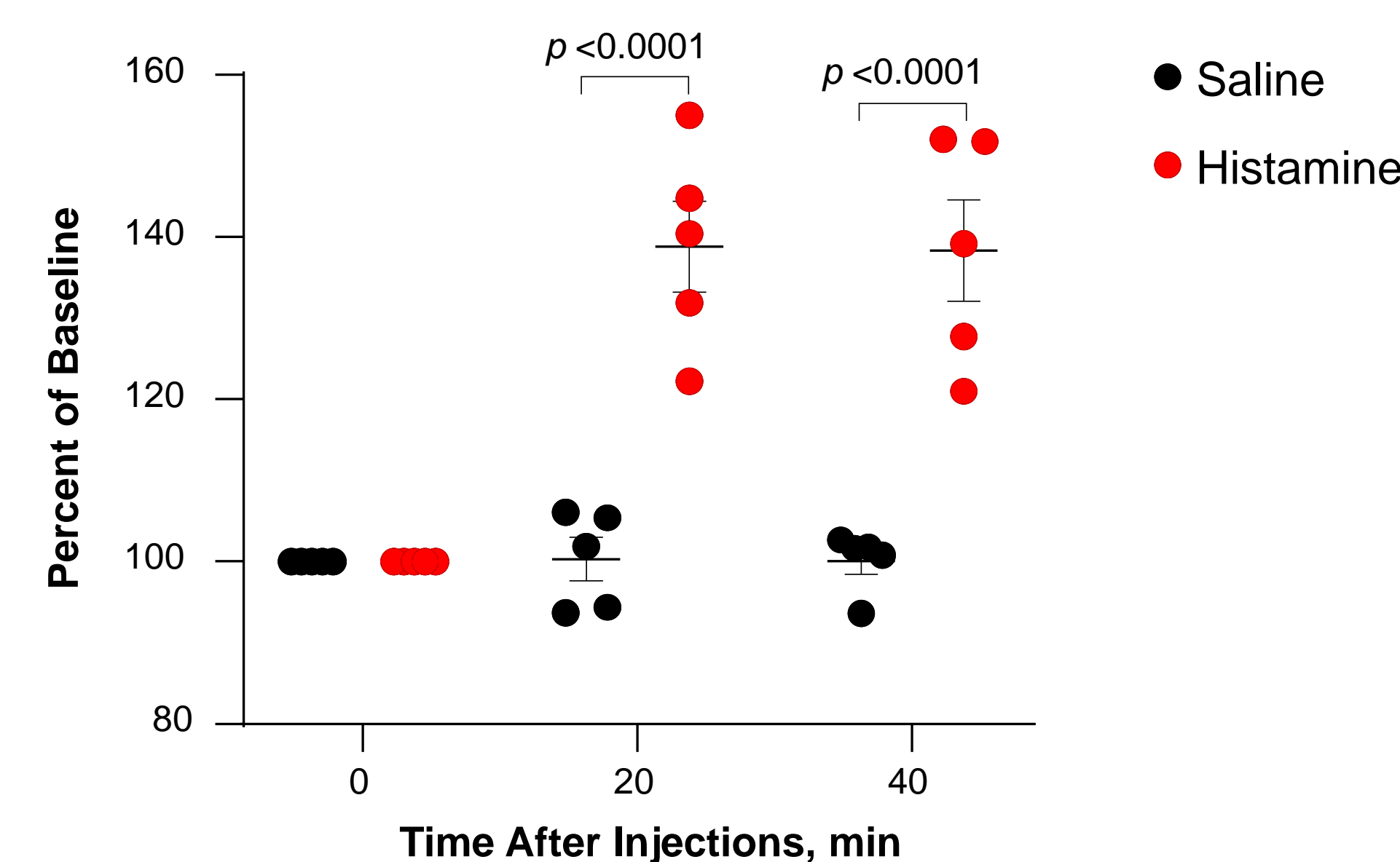
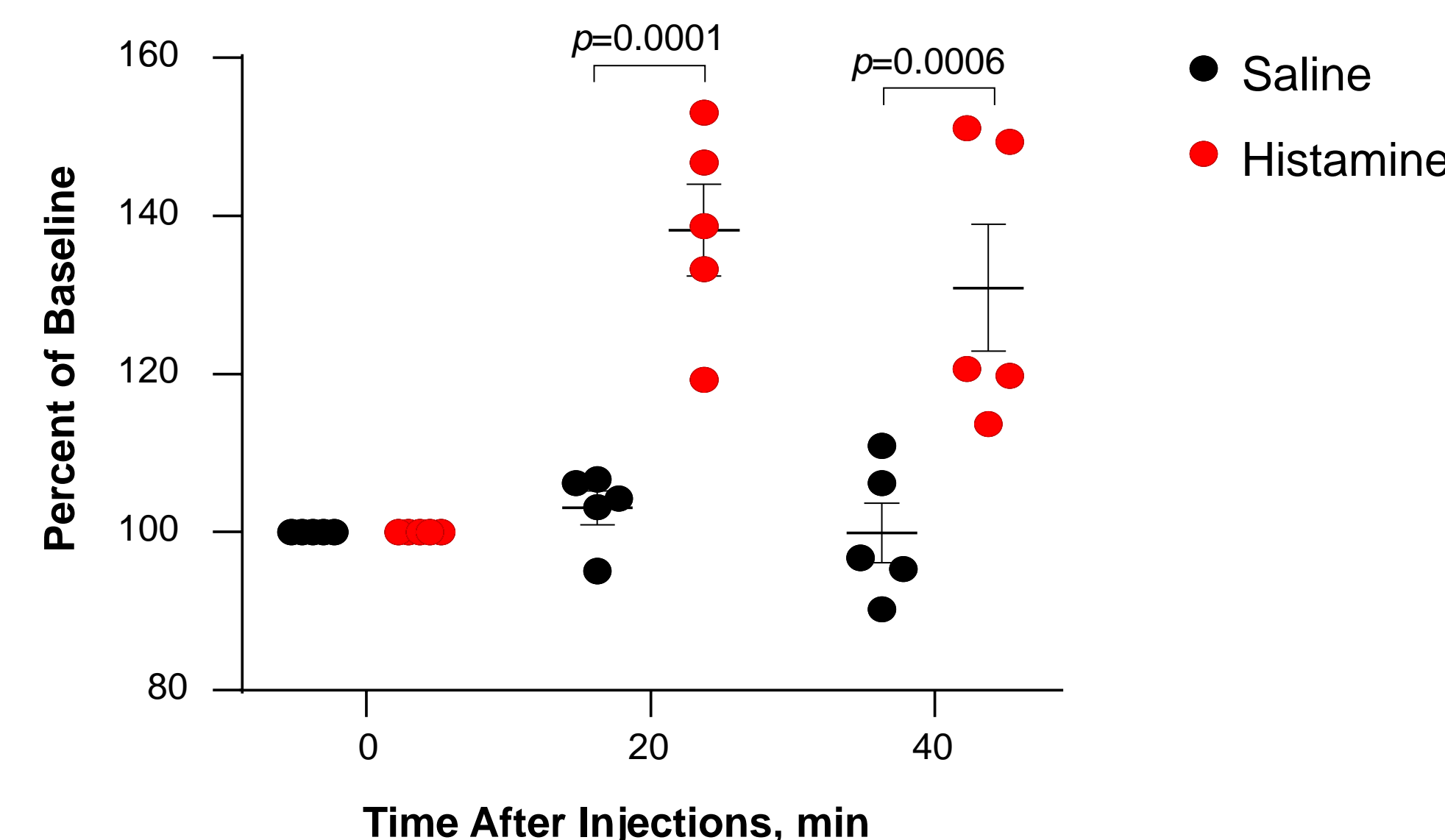


Figure 2: Tongue Thickness Over Time



For Figures 1 and 2:

- Horizontal lines are mean values, and error bars show standard error of the mean (SEM).
- P-values were calculated using ordinary one-way ANOVA with multiple comparisons.

POPULATION PHARMACOKINETIC DATA

Histamine-induced angioedema did not significantly alter the epinephrine PK profile for Anaphylm (Table 1 and Figure 3).

Table 1: Pharmacokinetic Parameters

	Saline + Anaphylm (n=5)	Histamine + Anaphylm (n=5)	p-value
Geometric mean C _{max} , ng/mL	8.82	7.77	0.4786 ^a
AUC ₀₋₄₈₀ ± SE, min·ng/mL	1729 ± 313.4	1551 ± 300.2	0.6907 ^a
Median T _{max} , min	90	120	0.3810 ^b
T _{max} range, min	60–120	40–180	--

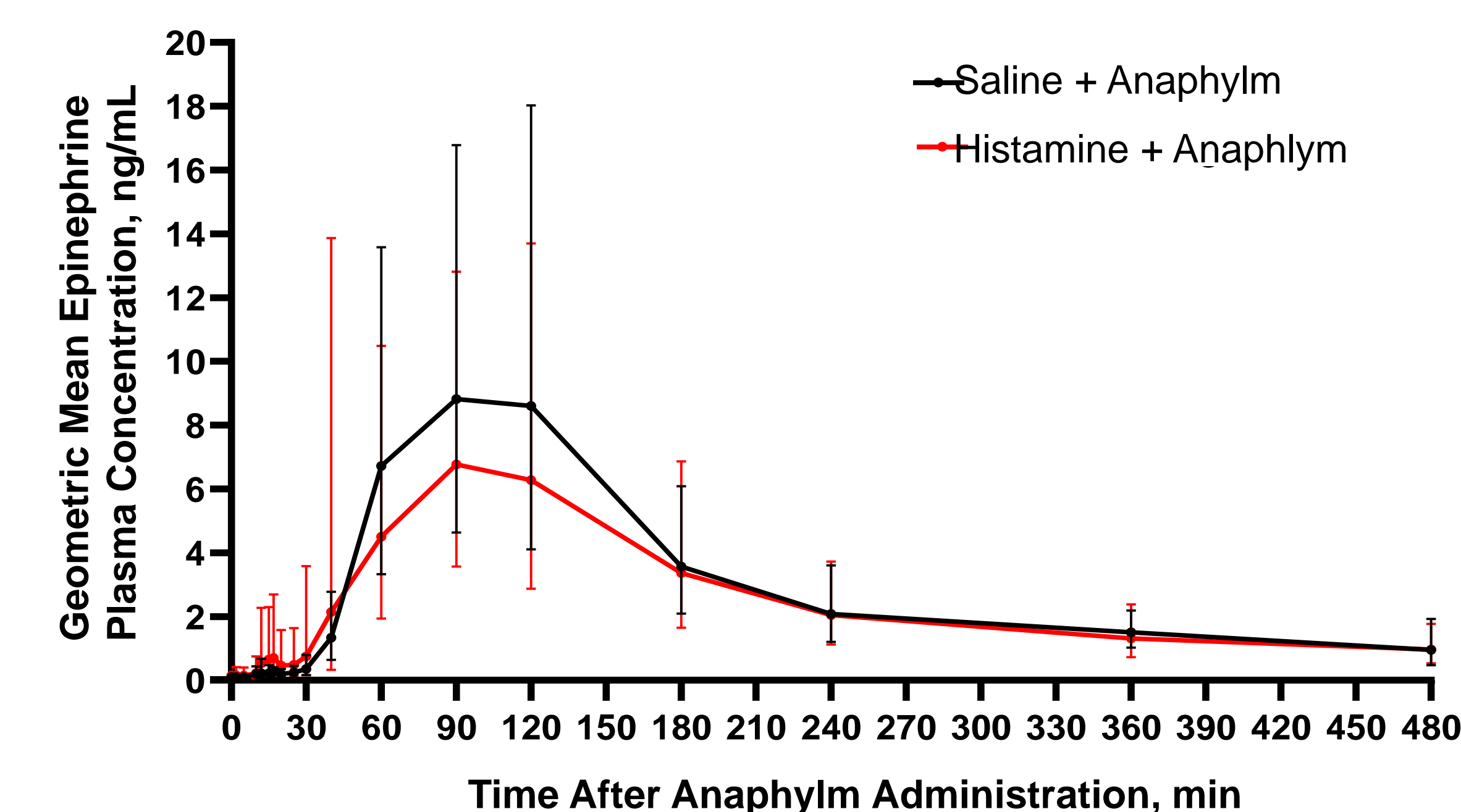
^aCalculated using unpaired t-test.

^bCalculated using Mann-Whitney test.

AUC, area under the curve; C_{max}, maximum concentration; SE, standard error;

T_{max}, time to C_{max}.

Figure 3: Epinephrine Plasma Concentration Over Time



CONCLUSION

- A novel animal model for the induction of oral angioedema and evaluation of the impact of the edema on sublingual absorption is presented.
- The preclinical data suggest that localized swelling of the oral mucosa results in increased absorption during early time points but is not likely to have a meaningful impact on the overall PK profile of epinephrine following Anaphylm administration.

REFERENCES

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DISCLOSURES

Dr.'s Wargacki and Slatko are employees of Aquestive Therapeutics. Dr. Haney and Mr. Klepner are employees of Altasciences Company.

