Novel Routes of Epinephrine Administration

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Novel Routes of Epinephrine

Learning Objectives:

1. Describe recent observations about standard epinephrine dose and delivery methods
2. Explain the PK and PD profiles of epinephrine treatment
3. Compare the features and profiles of novel epinephrine products

Epinephrine for anaphylaxis: Evidence base for treatment

- No controlled trials.
- Efficacy and safety of 0.01 mg/kg dose (up to 0.3 mg in children or 0.5 mg in adults) is based on empiric use for more than 50 years.
- Delayed administration is associated with increased likelihood of:
  - Need for additional doses
  - Biphasic anaphylaxis (Ellis 2007)
  - Hospitalization, ICU admission (Robinson 2017; Fleming 2015)
  - Fatal and near-fatal reactions (Bock 2001, Sicherer 2017)
- Recommended as essential first-line treatment of anaphylaxis by AAAAI, AAP, European, Australasian, Canadian, WAO, and WHO guidelines

In the beginning

1987


MEDICINE
NO NEEDLE
RAINER
PRACTICE
MEDICINE
NO NEEDLE
NER
PRACTICE ONLY

EAIs– Barriers to Use

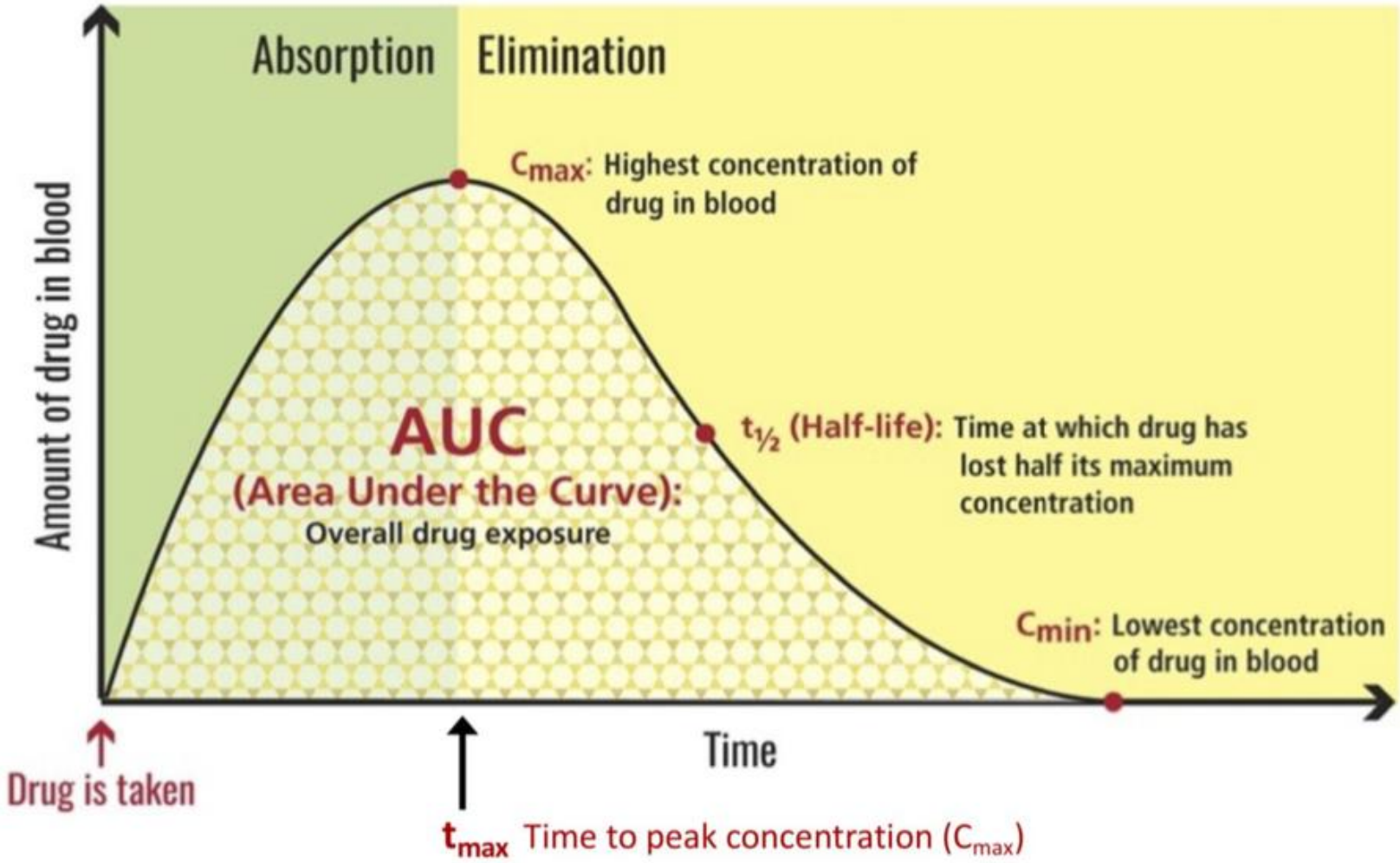
- Big needle!
- Need to go to ED
- Fear of side effects
- Inconvenient to carry
- High cost
- Limited shelf life
- Not sure if they need it (when to use it)
- Think diphenhydramine will work

Novel routes of epinephrine – needle free

- Novel routes
  - Nasal (spray or dry powder) – Neffy; Bryn-DISC, others
  - Sublingual film – Anaphylm
  - Inhaled? – in development
  - Transdermal (patch)? – exploratory (animal model)

- How do we know it will work?
  - Clinical trials (“infeasible; unethical”)
  - Compare with “gold standard” and approved products (bracketing)
    - Pharmacokinetics (best available surrogate for systemic activity)
    - Pharmacodynamics (best available surrogate for clinical efficacy)

Pharmacokinetics (PK)



Bioavailability of Auvi-Q compared with EpiPen

(Edwards et al. Ann Allergy Asthma Immunol 2013;111:132.)

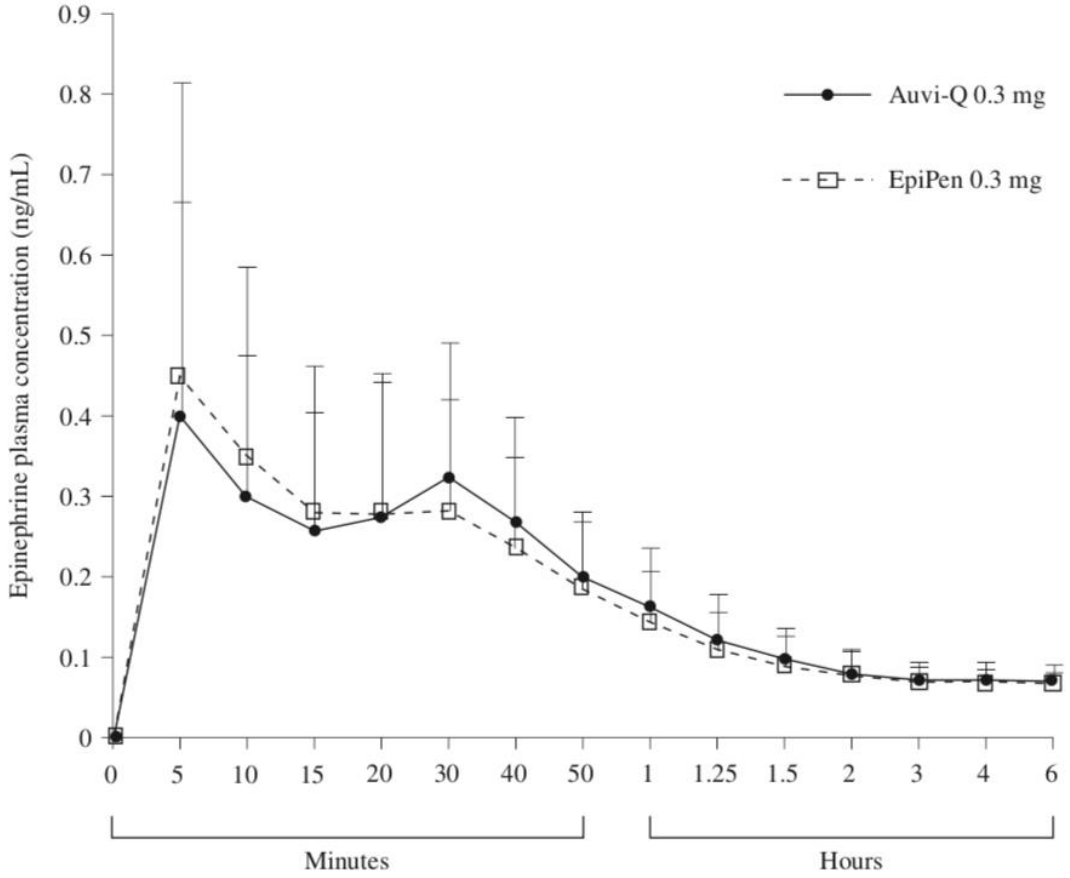


Table 3

T_{max} distribution by treatment group

Range of T_{max}, h	Treatment group, No. (%)			
	Reference 1[a] (n = 69)	Reference 2[a] (n = 66)	Test (n = 67)	Total (n = 202)
≥0 to <0.05	0	0	0	0
≥0.05 to <0.15	31 (45)	30 (45)	24 (36)	85 (42)
≥0.15 to <0.25	9 (13)	11 (17)	5 (7)	25 (12)
≥0.25 to <0.35	6 (9)	3 (5)	7 (10)	16 (8)
≥0.35 to <0.45	1 (1)	1 (2)	2 (3)	4 (2)
≥0.45 to <0.55	10 (14)	12 (18)	15 (22)	37 (18)
≥0.55 to <0.65	0	1 (2)	0	1 (0)
≥0.65 to <0.75	5 (7)	5 (8)	8 (12)	18 (9)
≥0.75 to <0.85	4 (6)	1 (2)	4 (6)	9 (4)
≥0.85 to <0.95	0	0	0	0
≥0.95 to ≤1	3 (4)	2 (3)	2 (3)	7 (3)

Tmax (min)

5

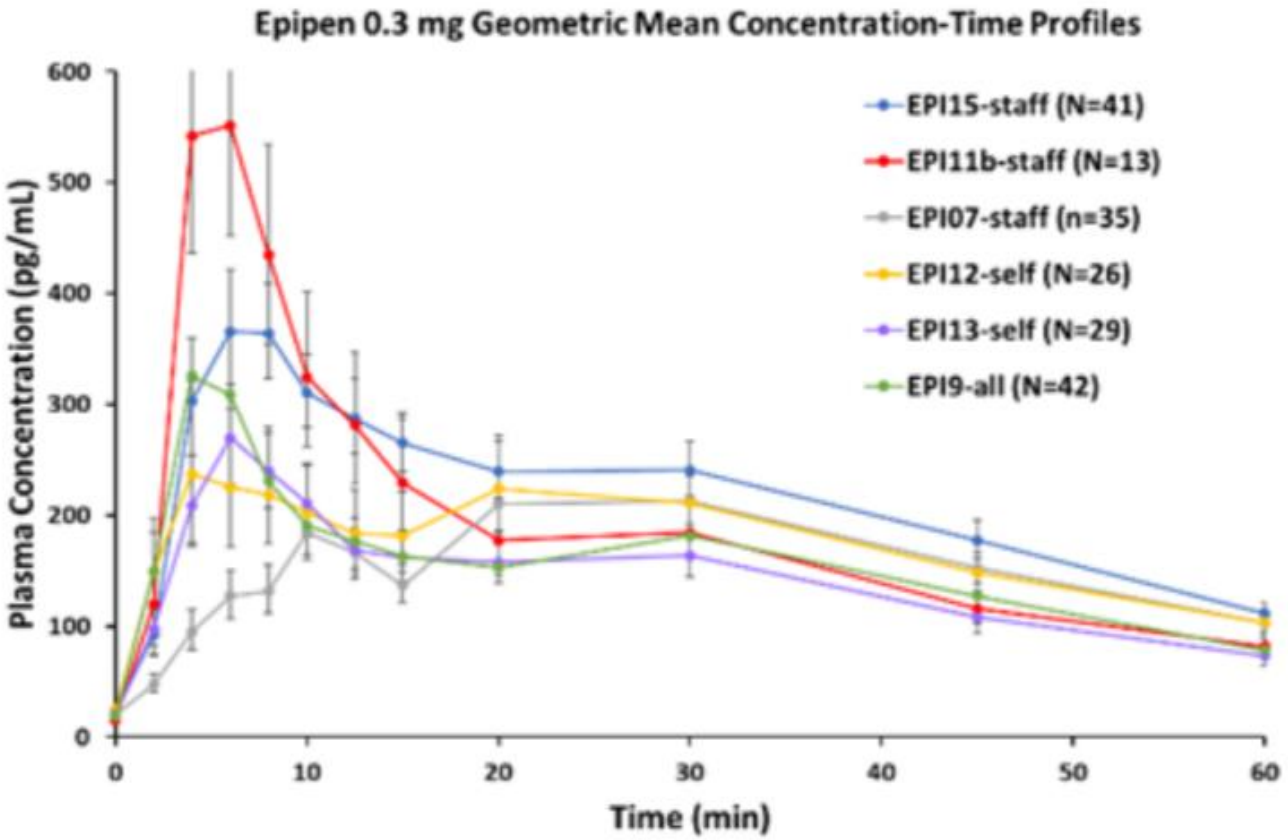
10

30

45

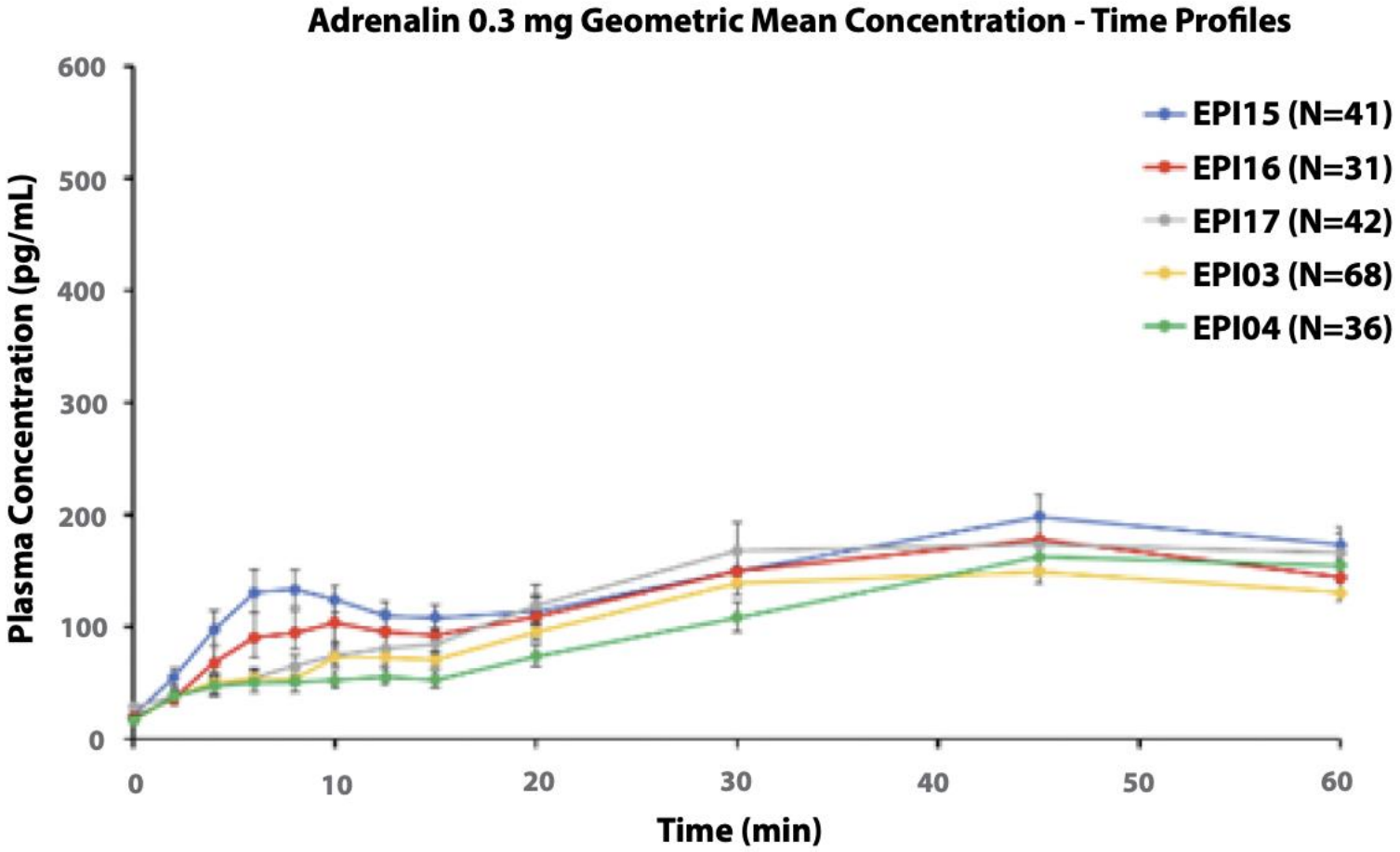
Epi-Pen Pharmacokinetics: Variability

A. Single-dose EpiPen 0.3 mg



ARS-1 NDA/BLA# 214697. FDA Briefing Document. May 11, 2023.

Epinephrine Pharmacokinetics:
Manual syringe and needle Intramuscular



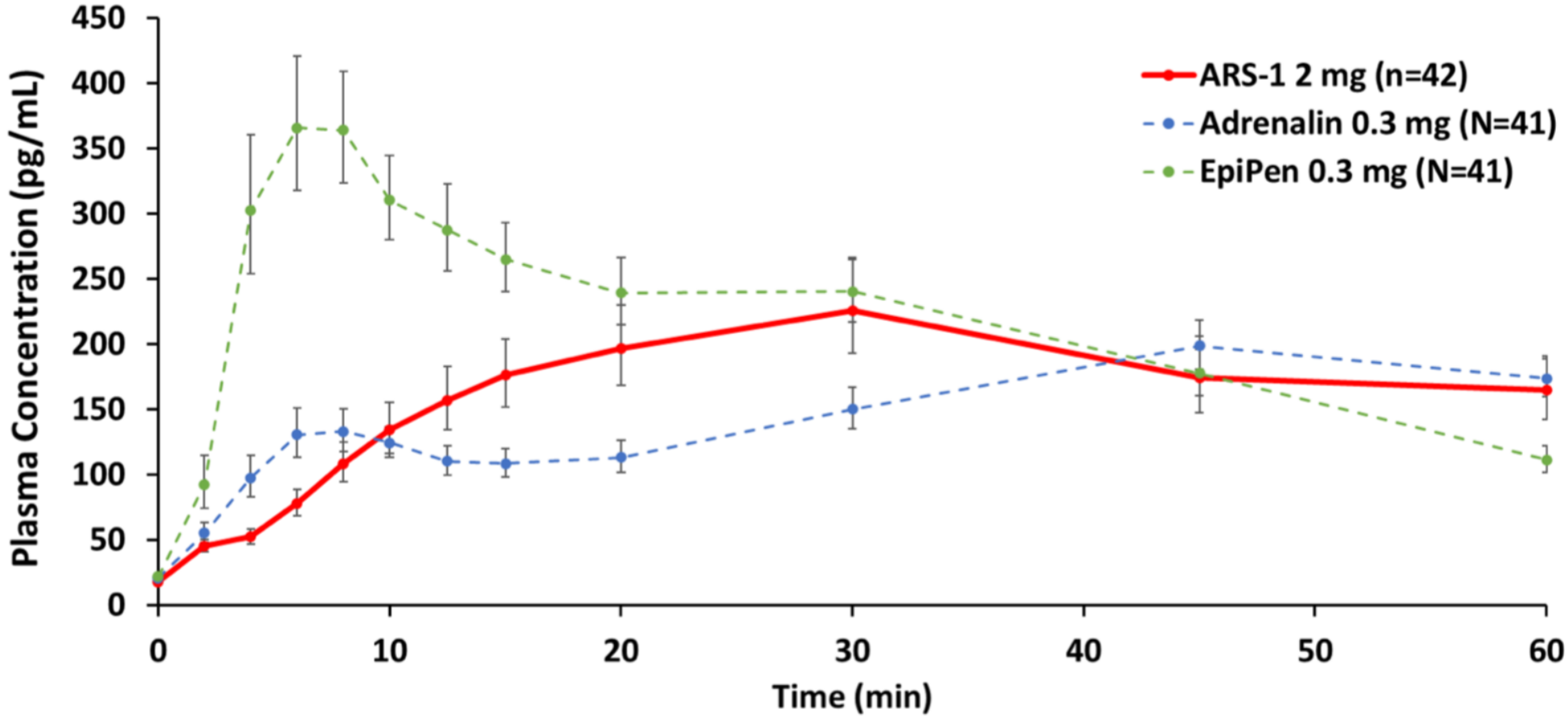
ARS-1 NDA/BLA# 214697. FDA Briefing Document. May 11, 2023.

Intranasal epinephrine

FDA-approved

August 9, 2024.

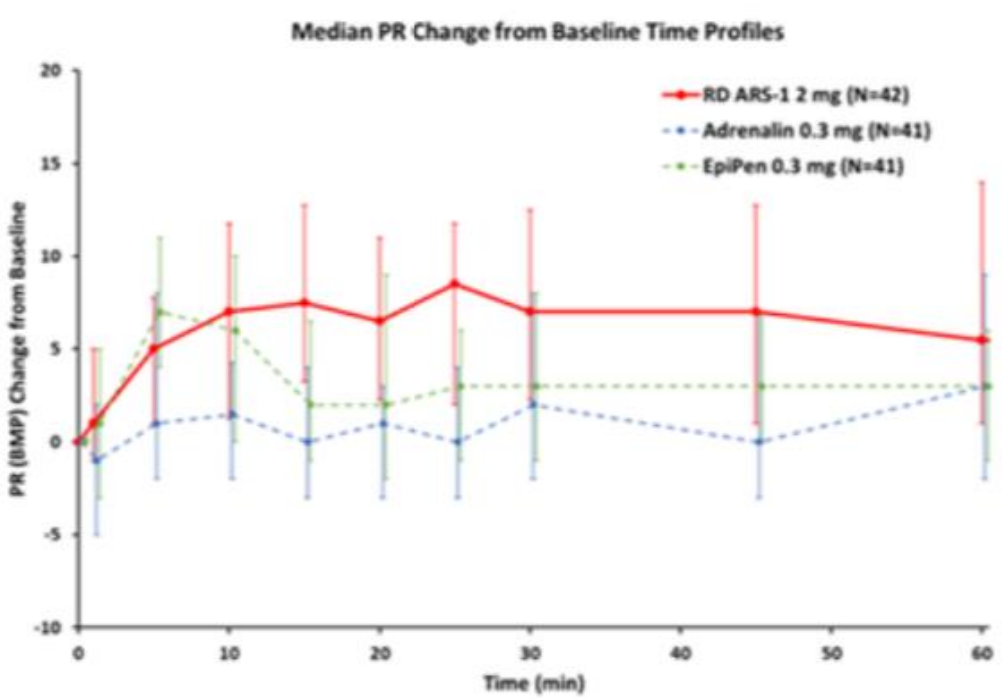
Figure 5. Epinephrine Geometric Mean (±Standard Error) Concentration-Time Profile Following a Single Dose of ARS-1 vs. a Single Dose of Intramuscular Injection Using Adrenalin 0.3 mg or EpiPen 0.3 mg in Healthy Subjects



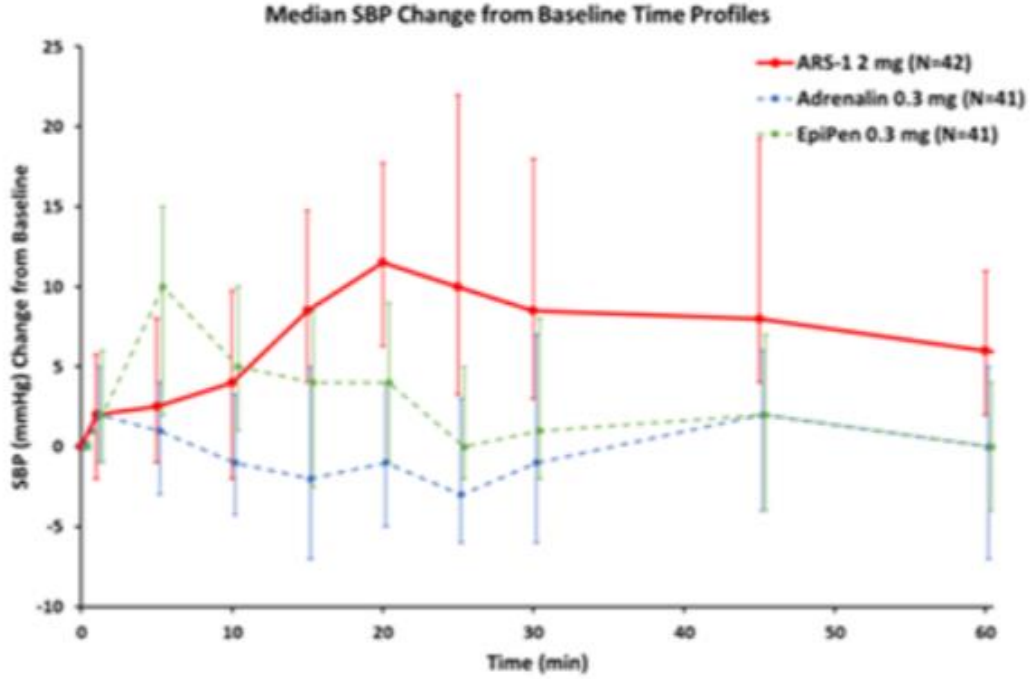
ARS-1 NDA/BLA# 214697. FDA Briefing Document. May 11, 2023.

Neffy Pharmacodynamics

Median PR change from baseline



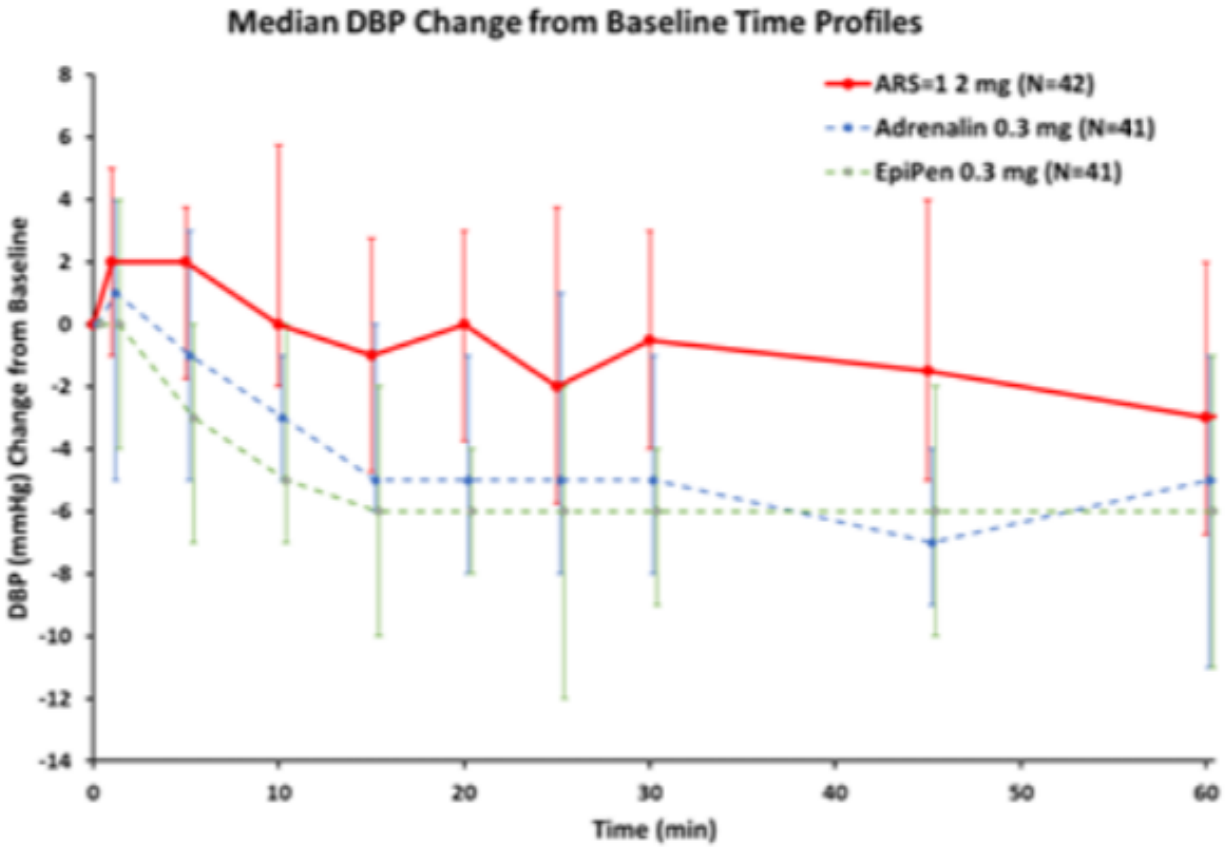
Median SBP change from baseline



ARS-1 NDA/BLA# 214697. FDA Briefing Document. May 11, 2023.

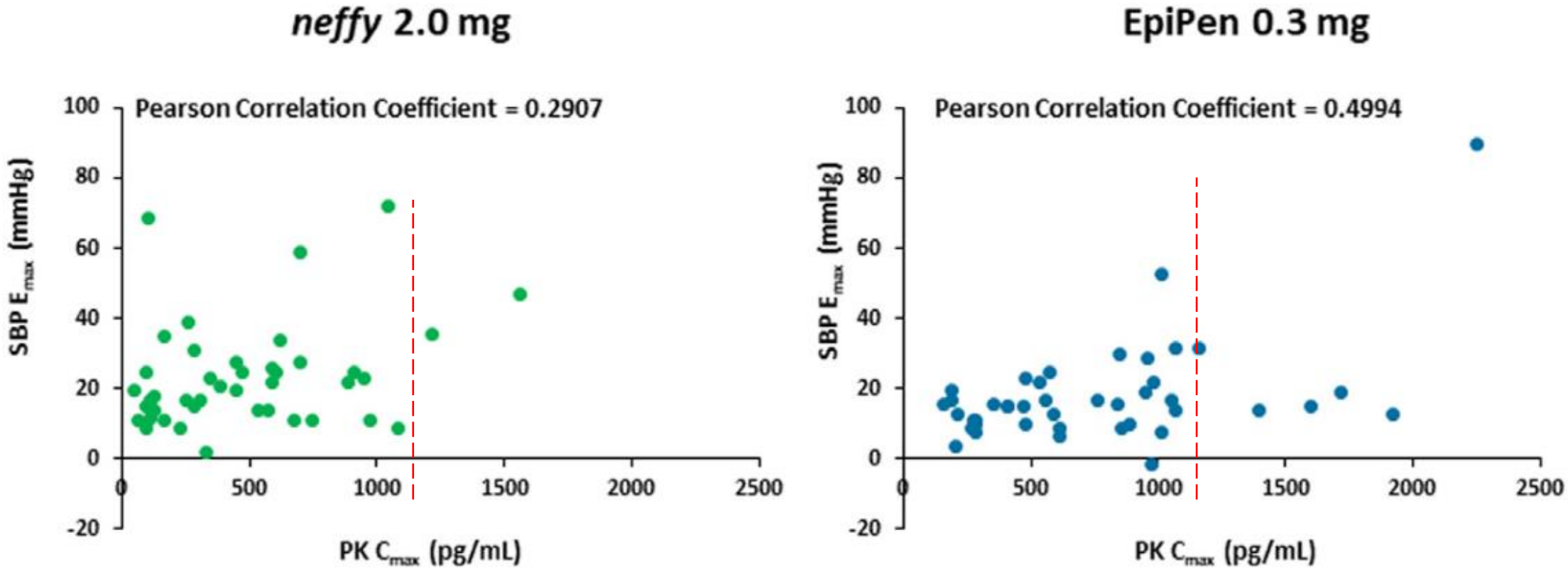
Neffy Pharmacodynamics: Diastolic BP

Median DBP change from baseline



ARS-1 NDA/BLA# 214697. FDA Briefing Document. May 11, 2023.

Epinephrine: How high is too high?

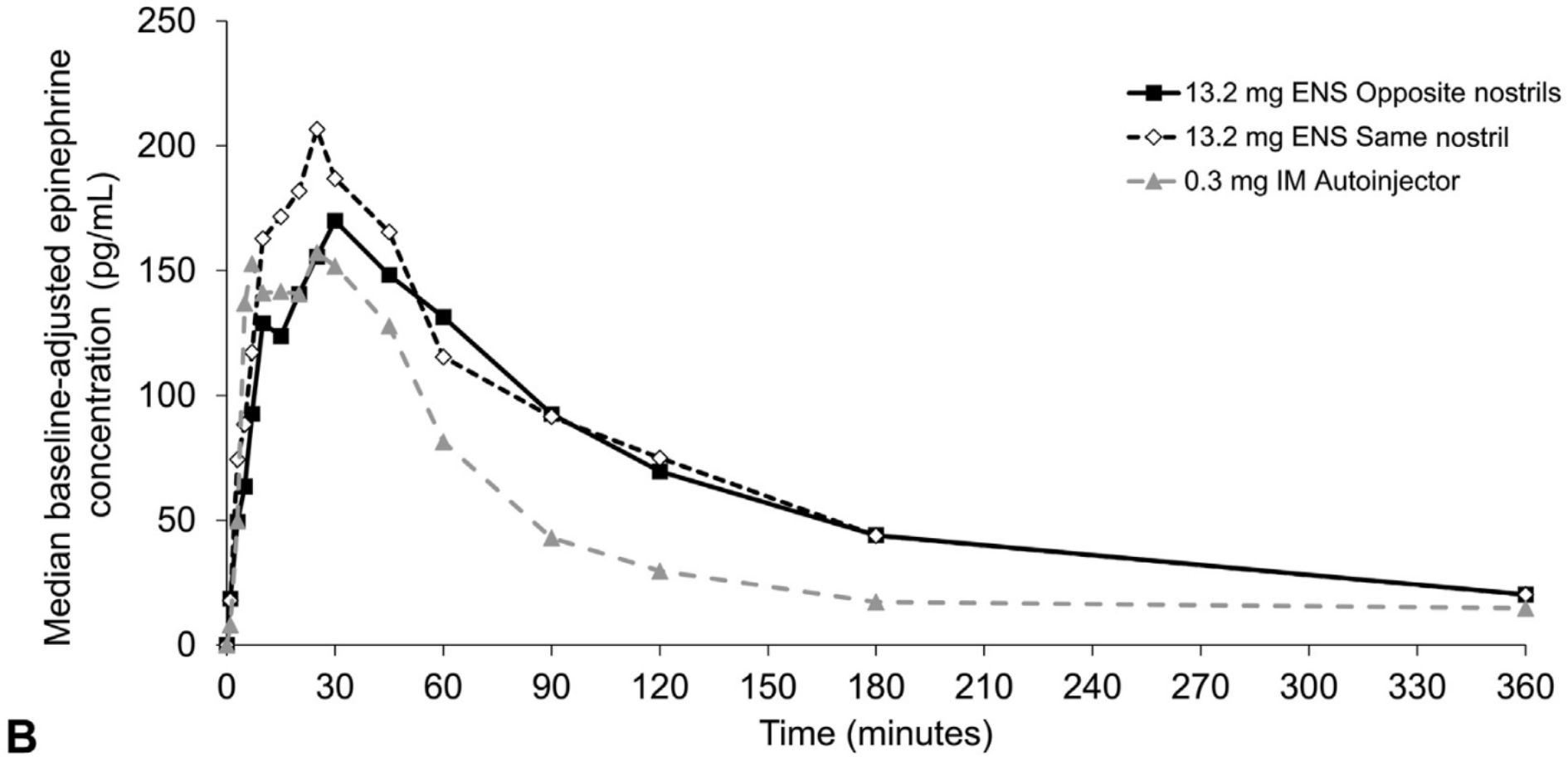


(Casale TB et al. JACI 2023;152;1587-96)

neffy Adverse effects

Adverse Reaction**	neffy 2 mg One Dose		neffy 2 mg Two Doses	
	N = 134		N = 85	
Throat irritation	2	(2%)	16	(19%)
Headache	8	(6%)	15	(18%)
Nasal discomfort	13	(10%)	11	(13%)
Feeling jittery	1	(1%)	9	(11%)
Tremor	0	(0%)	7	(8%)
Rhinorrhea	4	(3%)	6	(7%)
Nasal pruritus	0	(0%)	3	(4%)
Sneezing	0	(0%)	3	(4%)
Abdominal pain	1	(1%)	3	(4%)
Gingival pain	0	(0%)	3	(4%)
Hypoesthesia oral	0	(0%)	3	(4%)
Nasal Congestion	0	(0%)	2	(2%)
Dizziness	4	(3%)	2	(2%)
Nausea	4	(3%)	2	(2%)
Vomiting	3	(2%)	2	(2%)

BRYN Pharma 13.2 mg Nasal Spray: Pharmacokinetic profile



Greenhawt M, et al. J Allergy Clin Immunol Pract 2024;12:3274-82.

Subjects with AE (%)	13.2 mg no NAC	13.2 mg with NAC	IM EAI	IM manual syringe
Headache	32	36	0	12
Nausea	12	16	0	0
Oropharynx pain	0	4	0	0
Vomiting	4	16	0	0
Nasal discomfort	0	0	0	0
Upper abdom. pain	12	12	0	0
Injection site pain	0	0	4	4

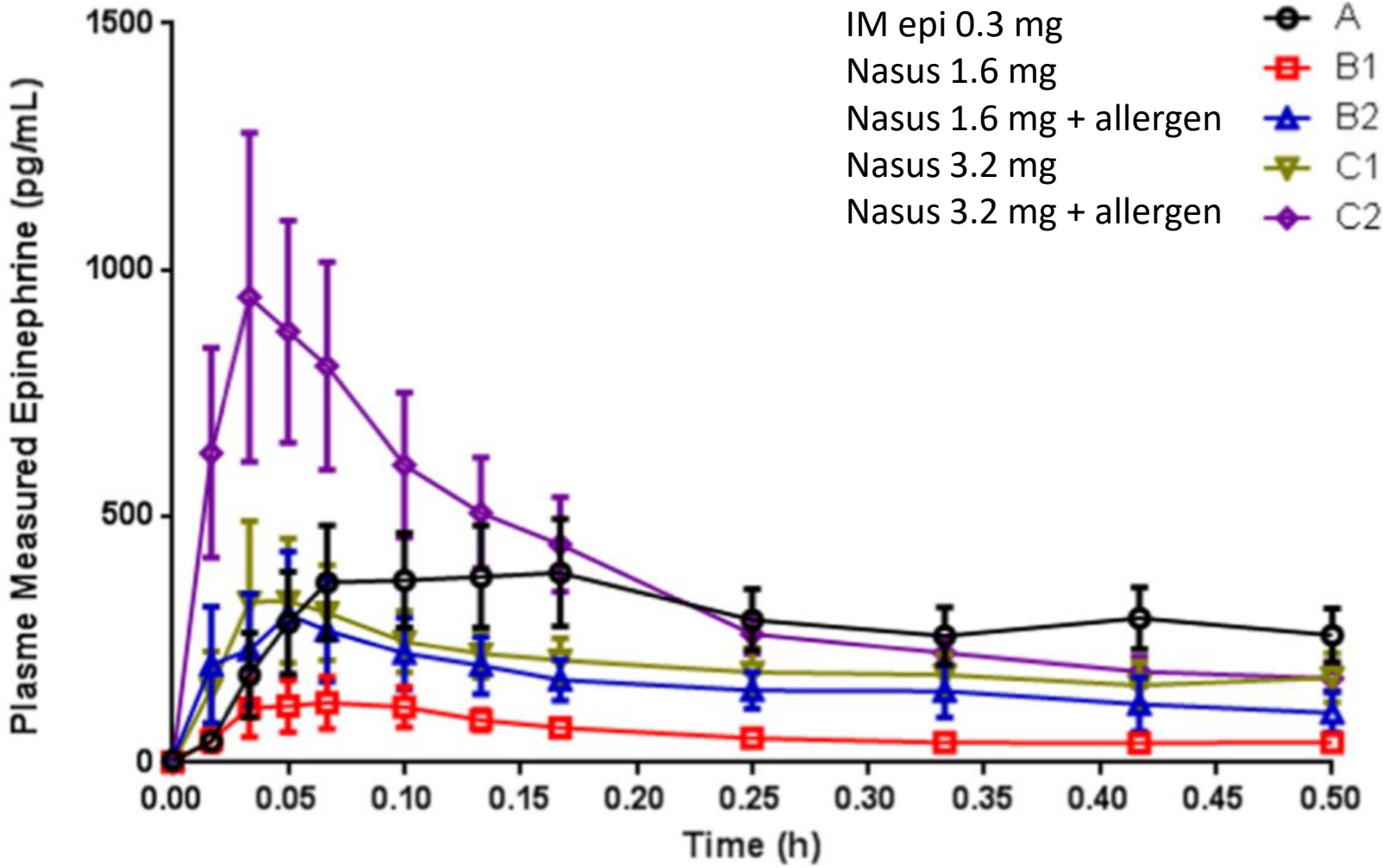
BRYN Pharma Nasal Spray: Randomized trial of 13.2 mg with nasal congestion

Adverse Events (same nostril)

Dworaczyk DA et al. Ann Allergy Asthma Immunol 2024;133:186-193.

Fast Acting, Dry Powder, Needle-Free, Intranasal Epinephrine Spray

Tal Y, et al . J Allergy Clin Immunol Pract. 2023 Jun 30:Epub PMID: 37394178.

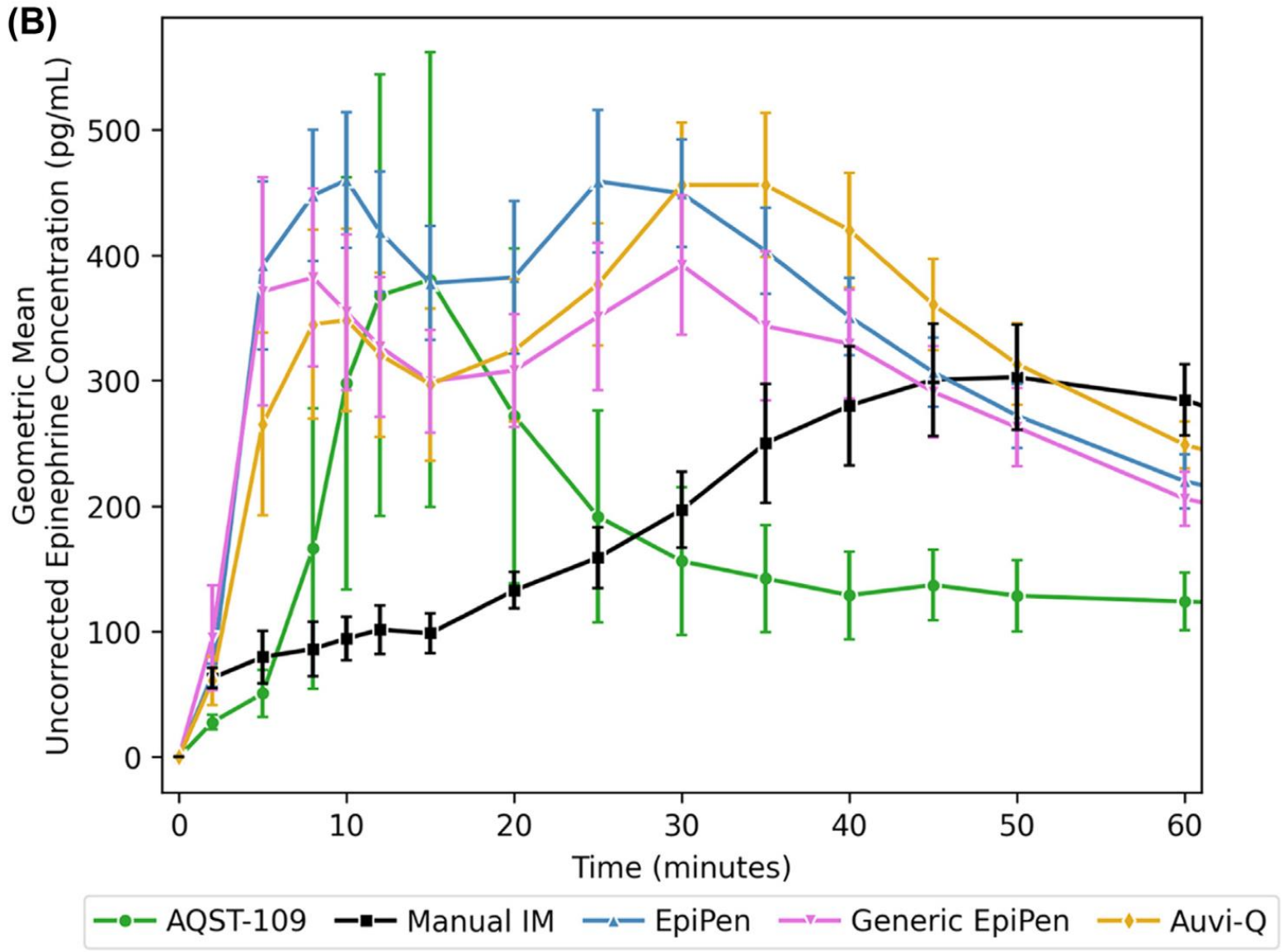


	Cmax	Tmax	AUC_{30min}
IM epi 0.3 mg	551	9.0	145
Nasus 1.6 mg	196	16.6	30.6
Nasus 1.6 mg + allergen	322	9.0	71.6
Nasus 3.2 mg	447	6.0	93.2
Nasus 3.2 mg + allergen	1110	2.5	185

Sublingual epinephrine

Anaphylm Pharmacokinetics

(Kraus CN et al. Ann Allergy Asthma Immunol 2025;134:580-586.)



Anaphylm Pharmacodynamics

Figure 4: Mean Change from Baseline in Pulse

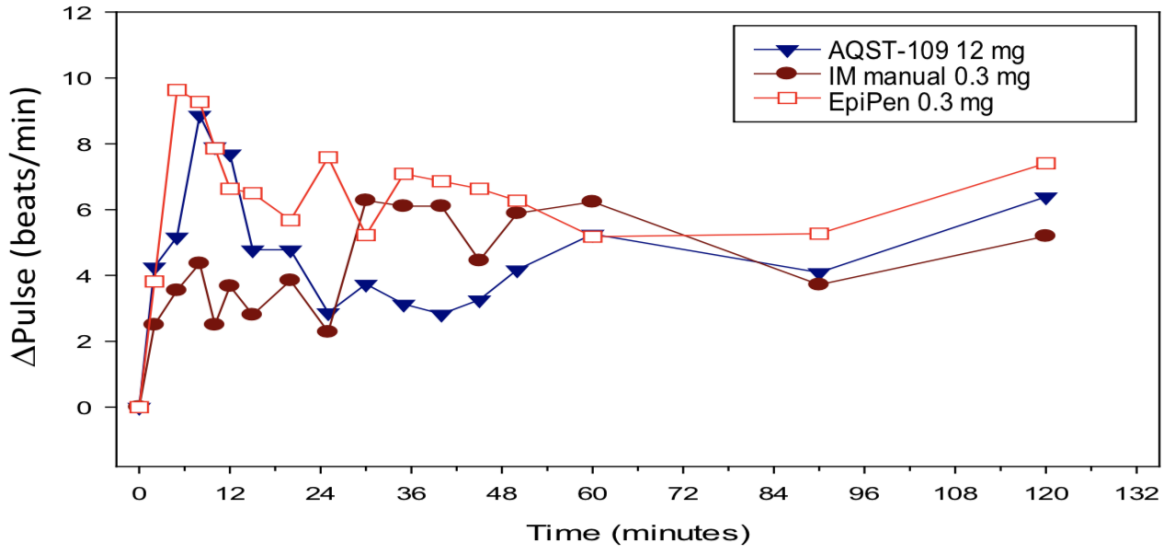
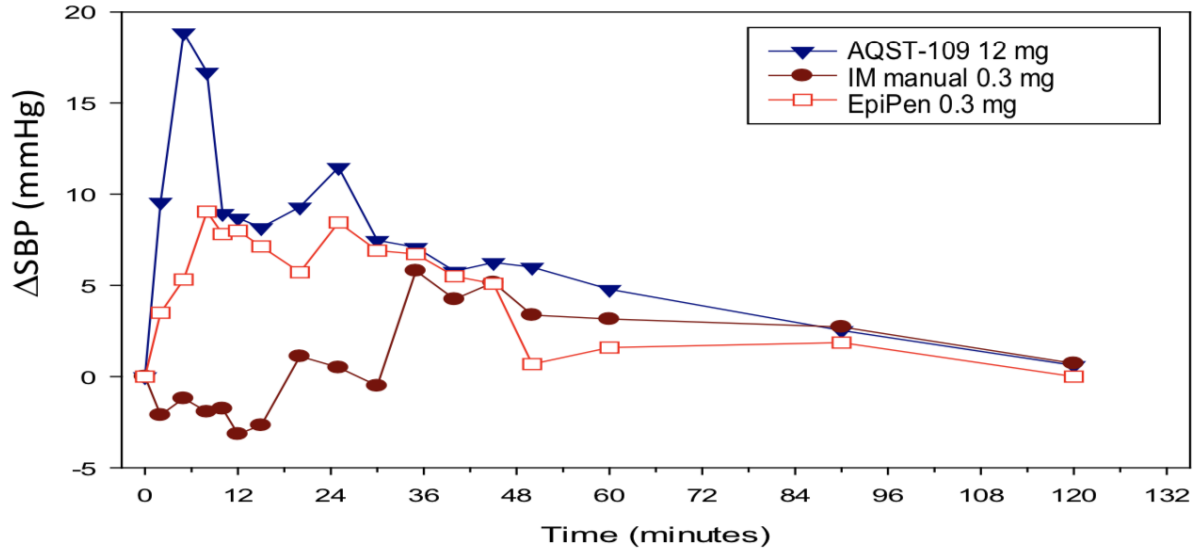


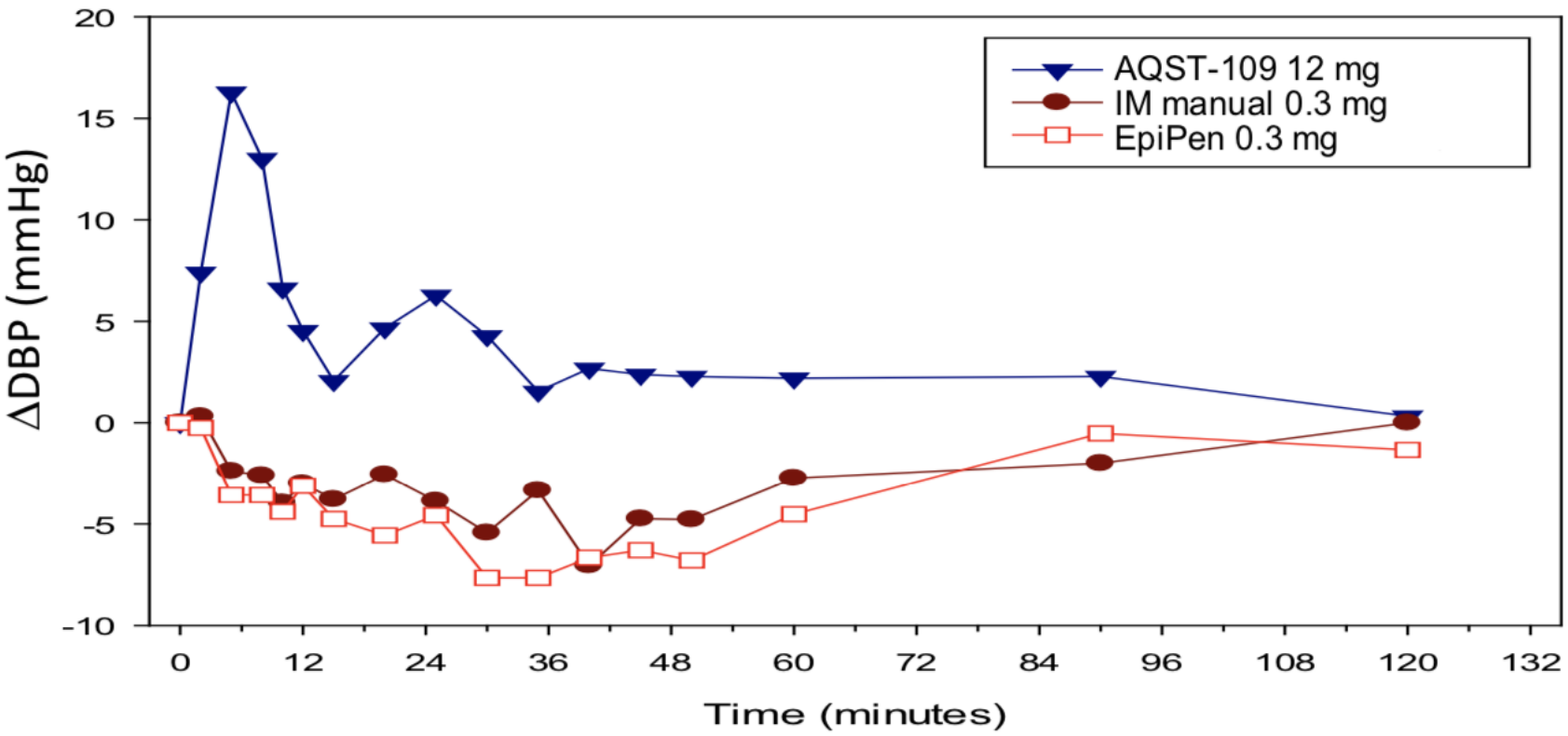
Figure 2: Mean Change from Baseline in Systolic Blood Pressure



Greenhawt et al.
Abstract AAAAI 2023

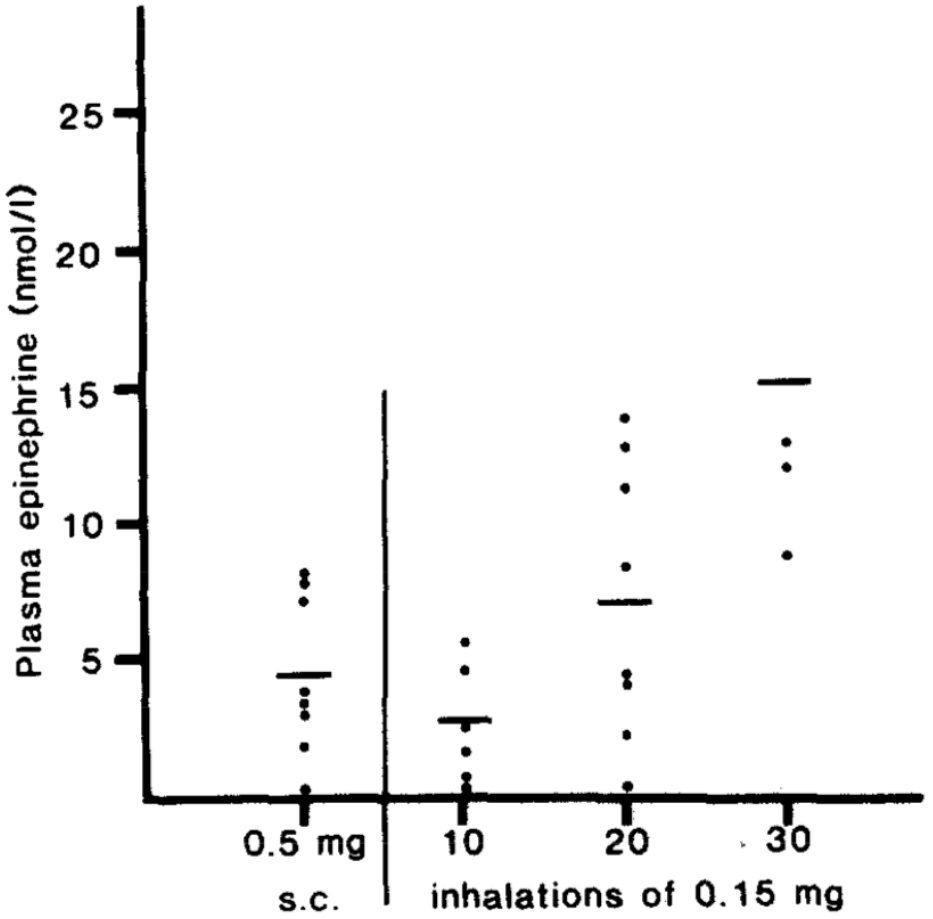
Anaphylm Pharmacodynamics

Figure 3: Mean Change from Baseline in Diastolic Blood Pressure



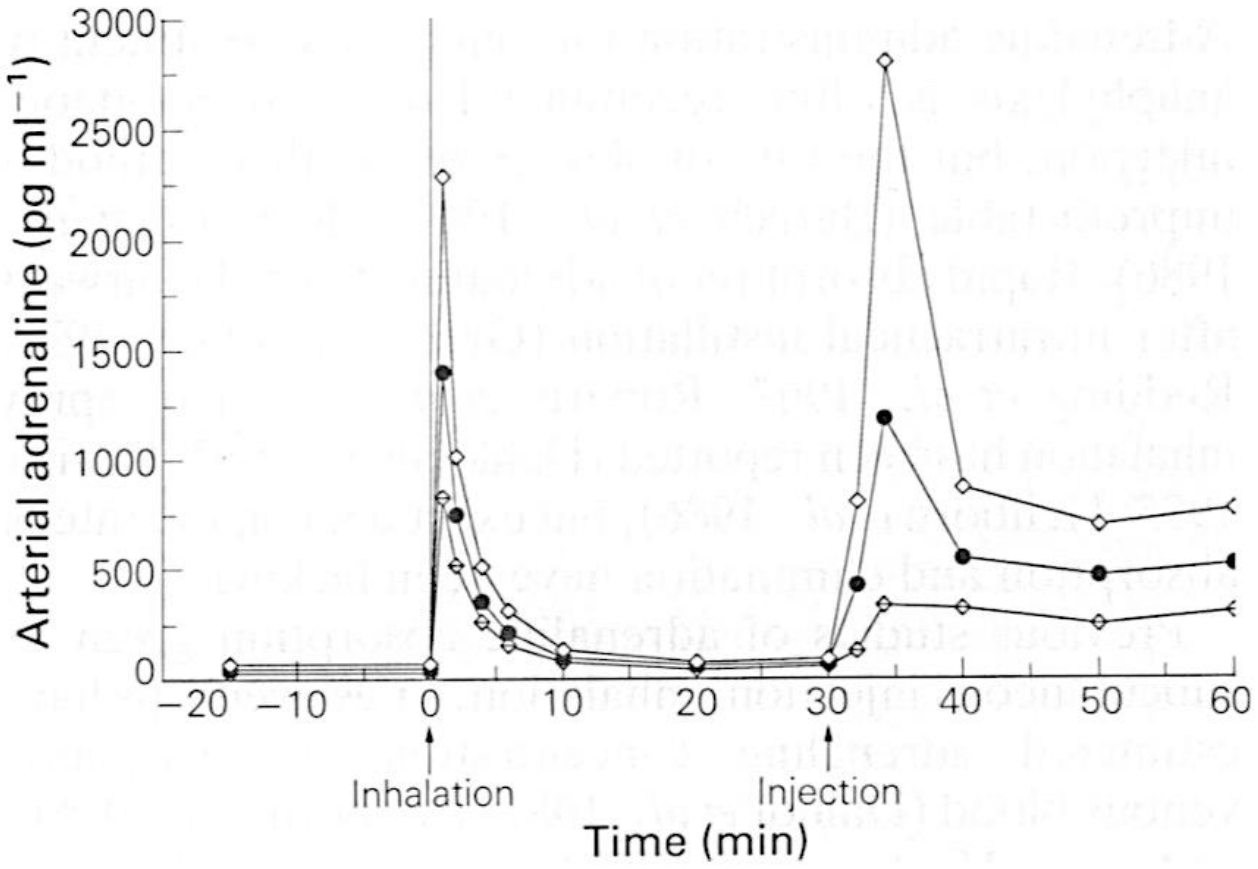
Greenhawt et al. Abstract AAAAI 2023

Comparison of subcutaneous injection and high-dose inhalation of epinephrine.



Heilborn H et al. J Allergy Clin Immunol 1986;78:1174-9

Faster and more reliable absorption of adrenaline by aerosol inhalation than by subcutaneous injection

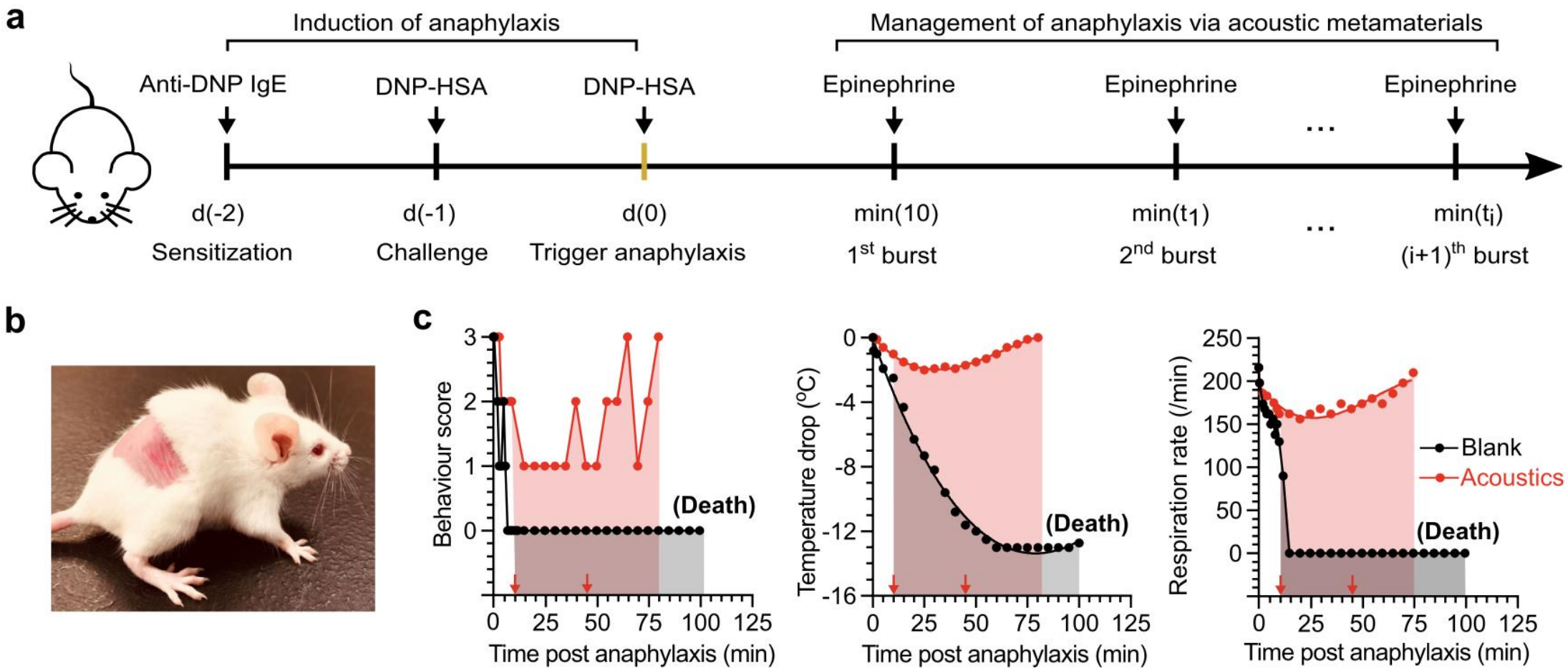


- **Inhalation** (20 puffs=3 mg)
  Tmax 1 min
  rapid decline
- **s/c injection** (0.5 mg)
  Tmax 4 min
  sustained level
- **Cmax** (median ± 95% CI)
  similar
- Less inter-subject variation by inhalation than by injection
- BP and HR follow concentration

Mellem H et al. Br J Clin Pharm 1991;31:677-681.

Acoustic metamaterials-driven transdermal drug delivery for rapid and on-demand management of acute disease.

Xu J et al. Nature Communications 2023;14:869.



But will it work?

Are PK and PD profiles sufficient to have confidence in the therapeutic effect?

What is a therapeutic serum level?
Is it the same for everyone?

How important are the Tmax and/or $T_{1/2}$?

Do we need clinical trials?

How?
- OFC?
- OIT?
- SCIT?
- ED?

Neffy for anaphylactic reactions during OFC

Ebisawa M et al. JACI 2024;153:AB371 (abstract)

- Patients age 6-17 with OFC causing anaphylaxis grade ≥2 (n = 15)
- Neffy 1 mg in patients 15-30 kg (n = 6)
- Neffy 2 mg in patient >30 kg (n = 9)
- 18 grade 2 reactions observed
- No 2nd dose needed within 15 min after 1st dose
- Median time to symptom resolution 16 min (range 1-90 min)
- 1 biphasic reaction 2.75 hours after 1st dose
- 7 patients had AEs – mild-moderate; most resolved quickly

Novel Routes of Epinephrine Administration

- Products for epinephrine delivery by novel routes show pharmaco-kinetic and pharmacodynamic similarities to injected epinephrine.
- Novel routes of epinephrine show some PK and PD differences from IM epinephrine in onset of action and duration of action.
- Novel routes of epinephrine should enable earlier and more frequent epinephrine use, leading to reduced morbidity and reduced need for hospital care.

“ THE THINGS WE NEVER CHALLENGE

ARE THE THINGS THAT NEVER CHANGE ”

James Keelaghan (Turn of the Wheel, 1995)

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