Ann Allergy Asthma Immunol 130 (2023) 508–514

Contents lists available at ScienceDirect

Pharmacokinetic and pharmacodynamic comparison of epinephrine, administered intranasally and intramuscularly

An integrated analysis

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ARTICLE INFO

Article history:
Received for publication August 17, 2022.
Received in revised form October 7, 2022.
Accepted for publication October 27, 2022.

ABSTRACT

Background: Manual intramuscular epinephrine injection is the standard of care for treating severe allergic reactions and anaphylaxis. Epinephrine autoinjectors were approved on the basis of the assumption that their pharmacokinetic and pharmacodynamic profiles are equivalent to manual intramuscular injection; however, although there is emerging evidence for product-related differences in pharmacokinetic profiles, very little is known about the comparative pharmacodynamic profiles.

Objective: To compare pharmacokinetic and pharmacodynamic profiles of epinephrine delivered through manual intramuscular injection, autoinjectors, and intranasal spray.

Methods: This integrated analysis was based on data from 4 randomized cross-over phase 1 trials that compared the pharmacokinetics and pharmacodynamics of epinephrine using manual intramuscular epinephrine 0.3 mg injection, epinephrine 0.3 mg autoinjectors (Symjepi and EpiPen), and epinephrine 1 mg intranasal spray (neffy).

Results: Data from 175 participants showed that although neffy (1.0 mg intranasal spray) resulted in a maximum concentration (258 pg/mL) that was lower than or comparable with manual epinephrine intramuscular injection (254 pg/mL), Symjepi (438 pg/mL) and EpiPen (503 pg/mL), it led to comparable increases in systolic blood pressure (maximum effect [E_{max}], 16.9, 10.9, 14.9, and 18.1 mm Hg, respectively). The effect of neffy on diastolic blood pressure was also markedly more pronounced than that of other products (E_{max}, 9.32, 5.51, 5.78, and 5.93 mm Hg, respectively).

Conclusion: Intranasal delivery of epinephrine using neffy increases systolic blood pressure more efficiently than do manual intramuscular injection and epinephrine autoinjectors, despite lower maximum plasma concentrations.

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Introduction

Clinically, epinephrine appears to work rapidly after systemic administration, regardless of the route of administration and device or device-related differences in pharmacokinetics. The labels of approved epinephrine products have similar "indication and usage," "dosage and administration," "warning and precaution," and "adverse reactions" sections, and the guidelines for the treatment of anaphylaxis do not differ on the basis of the type of epinephrine product being used. Although studies indicate that there are pharmacokinetic differences between epinephrine outoinjectors (EAIs) including EpiPen and manual intramuscular epinephrine injection,[1–3] the corresponding differences in pharmacodynamic parameters have not been assessed.

A novel intranasal epinephrine spray (neffy; ARS Pharmaceuticals, Inc) is being developed as a potential alternative to intramuscular epinephrine administration. The objective of this analysis was to assess the pharmacokinetic and pharmacodynamic differences between intranasal epinephrine spray and other available EAIs and manual intramuscular epinephrine injection.

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Disclosures: Dr Tanimoto and Mr Lowenthal are employees of ARS Pharmaceuticals, Inc. Dr Kaliner and Dr Lockey received remuneration for serving in an advisory/consulting role from ARS Pharmaceuticals, Inc. Dr Ebisawa received honoraria from Mylan (now Viatris, Inc) and ARS Pharmaceuticals, Inc. Dr L.P. Koplowitz and Dr B. Koplowitz have no conflicts of interest to report.

Funding: This study was funded by ARS Pharmaceuticals, Inc. The sponsor participated in design and conduct of the study, writing the manuscript, and the decision to submit the manuscript for publication.

https://doi.org/10.1016/j.anai.2022.10.024
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Methods

Study Design and Population

An integrated analysis was performed using data from 4 randomized, open-label, single-dose phase 1 trials that compared the pharmacokinetic and pharmacodynamic profiles of intranasal epinephrine 1 mg spray (neffy; ARS Pharmaceuticals, Inc) with manual epinephrine intramuscular injection 0.3 mg (Epinephrine 0.3 mg intramuscular [IM]), EpiPen 0.3 mg (Mylan, Canonsburg, Pennsylvania), and Symjepi 0.3 mg (Adamis, San Diego, California) injected into the anterolateral thigh per their labels. Two studies enrolled healthy individuals aged 19 to 55 years, and 2 studies enrolled healthy volunteers with a history of type I allergies (allergic rhinitis, food allergy, venom allergy), aged 19 to 55 years. Pharmacodynamics after placebo intramuscular injection into the anterolateral thigh was used as a control. The study protocols were approved by the Institutional Review Boards (IRB) or Ethics Committees of the study sites, including Novum IRB and Integ Review IRB, and all participants gave written informed consent before participation in the studies. The studies were conducted according to the International Conference on Harmonization Guidelines for Good Clinical Practice.

Pharmacokinetic and Pharmacodynamic Analysis

Blood samples were collected before dosing and up to 480 minutes after dosing. Plasma epinephrine concentrations were determined from the blood samples using a validated liquid chromatography-mass spectrometry and mass spectrometry method with a range of quantitation of 20.0 to 4000 pg/mL. Epinephrine concentration and pharmacokinetic (PK) parameters were calculated without the subtraction of the predose epinephrine concentrations because the absolute plasma levels are considered more important clinically to elicit an efficacious response. Individual PK parameters included area under the curve to the final time with a concentration equal to or greater than the lower limit of quantitation (AUC_{0-t}), maximum plasma concentration (C_{max}), and time to maximum plasma concentration (T_{max}), and were calculated from concentration-time data using noncompartmental methods.

Pharmacodynamic measurements (systolic blood pressure, diastolic blood pressure, and heart rate) were assessed before dosing and at various time points up to 120 minutes after dosing. Pharmacodynamic data were expressed as change from baseline (ΔBaseline), where baseline was the mean of the 2 predose measurements and ΔBaseline = value (at each time) − value (predose). Maximum effect (E_{max}), time to maximum effect (TE_{max}), and the relationship between C_{max} and E_{max} were analyzed to investigate the reasons for the observed pharmacodynamic differences between the epinephrine products.

Of note, the peak of mean plasma concentration vs time is not necessarily equal to the mean C_{max} because the mean plasma concentration is the average epinephrine concentration at each time point, whereas the mean C_{max} is the mean of highest epinephrine concentration for each subject. This is also the case for pharmacodynamics (PD) vs time and PD parameters (E_{max}).

Statistical Analysis

For all studies, PK plasma-concentration time data and PD time data were analyzed using noncompartmental methods in Phoenix™ WinNonlin (Version 8.1 or higher, Certara, LP) in conjunction with the internet-accessible implementation of Pharsight Knowledgebase Server (PKSO; Version 4.0.4 or higher, Certara, LP).

Results

Baseline Demographics

Data from 175 study participants was included in this integrated PK analysis. Baseline variables (ie, age, sex, height) were balanced between groups (eTable 1).

Pharmacokinetics

The epinephrine concentration vs time curve showed the highest mean epinephrine concentration after administration through EpiPen, followed by Symjepi, neffy, and Epinephrine 0.3 mg IM (Fig 1). The highest mean C_{max} values were observed after EpiPen (503 pg/mL) and Symjepi (438 pg/mL). The mean C_{max} of neffy (258 pg/mL) was comparable with Epinephrine 0.3 mg IM (254 pg/mL) (Table 1, Fig 1). The longest median time to maximum concentration occurred after Epinephrine 0.3 mg IM (45 minutes), followed by Symjepi (30 minutes), neffy (30 minutes), and EpiPen (20 minutes) (Table 1).

Pharmacodynamics

Systolic Blood Pressure

EpiPen, Symjepi, and neffy resulted in comparable increases in mean systolic blood pressure (SBP) vs time, whereas the change with Epinephrine 0.3 mg IM was less pronounced. The highest mean SBP E_{max} was observed after EpiPen (18.1 mm Hg), followed by neffy (16.9 mm Hg), Symjepi (14.9 mm Hg), and Epinephrine 0.3 mg IM (10.9 mm Hg) (Table 2, Fig 2). Systolic blood pressure TE_{max} was longest after Epinephrine 0.3 mg IM (30.5 minutes), followed by neffy (21.0 minutes), EpiPen (18.0 minutes), and Symjepi (16.0 minutes).

Diastolic Blood Pressure

neffy was the only product that resulted in an increase in mean diastolic blood pressure (DBP) over time. All injection products resulted in a decrease in DBP, with the magnitude of decrease after epinephrine injection being greater than that observed after placebo (Fig 2). The greatest mean DBP E_{max} was observed after neffy (9.32 mm Hg). Relative to the increase in DBP after neffy, increase of DBP E_{max} values was suppressed after all injection products: Epinephrine 0.3 mg IM (5.51 mm Hg), Symjepi (5.78 mm Hg), and EpiPen (5.93 mm Hg) (Table 2). The longest DBP TE_{max} was observed after EpiPen (25.0 minutes), followed by Symjepi (18.0 minutes), neffy (15.0 minutes), and Epinephrine 0.3 mg IM (8.99 minutes). The

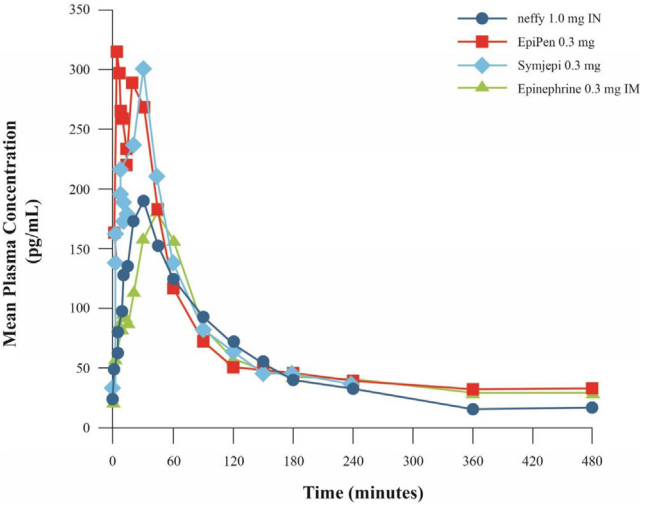

Figure 1. Mean plasma epinephrine concentration vs time after neffy, EpiPen, and Symjepi, Epinephrine 0.3 mg IM. IM, intramuscular; IN, intranasal.

Table 1
Comparison of Integrated Pharmacokinetic Parameters Across After neffy, Epinephrine 0.3 mg Intramuscular Injection, EpiPen, and Symjepi

Product	N	C_{max} (pg/mL) Mean (CV%)	AUC_{0-t} (min x pg/mL) Mean (CV%)	Median T_{max} (min) (range)
neffy 1.0 mg	135	258 (69.8)	23,700 (59.1)	30 (2-150)
Epinephrine 0.3 mg IM	104	254 (58.4)	27,200 (38.4)	45 (3.90-360)
Symjepi 0.3 mg	36	438 (64.6)	23,700 (37.5)	30 (4-90)
EpiPen 0.3 mg	71	503 (73.5)	27,900 (43.9)	20 (3-154)

Abbreviations: AUC_{0-t}, area under the concentration-time curve from 0 to time t; C_{max}, maximum concentration; CV, coefficient of variation; T_{max}, time to maximum concentration.

Table 2
Integrated E_{max} and TE_{max} by treatment

Product	N	E_{max} Mean (SD)			TE_{max} Median (range)		
		SBP (mm Hg)	DBP (mm Hg)	HR (bpm)	SBP (min)	DBP (min)	HR (min)
neffy 1.0 mg	100	16.9 (10.9)	9.32 (7.46)	13.6 (9.12)	21.0 (0.970-119)	15.0 (0.830-119)	20.0 (2.00-120)
Epinephrine 0.3 mg IM	68	10.9 (7.29)	5.51 (5.88)	12.8 (7.61)	30.5 (0.970-120)	8.99 (0.970-120)	30.0 (1.97-120)
Symjepi 0.3 mg	36	14.9 (11.4)	5.78 (6.45)	8.86 (8.53)	16.0 (4.00-115)	18.0 (4.00-115)	16.0 (5.00-85.0)
EpiPen 0.3 mg	71	18.1 (10.1)	5.93 (6.23)	14.4 (10.2)	18.0 (4.98-119)	25.0 (4.00-119)	14.0 (4.00-115)

Abbreviations: bpm, beats per minute; CV, coefficient of variation; DBP, diastolic blood pressure; E_{max}, maximum effect; HR, heart rate; SBP, systolic blood pressure.

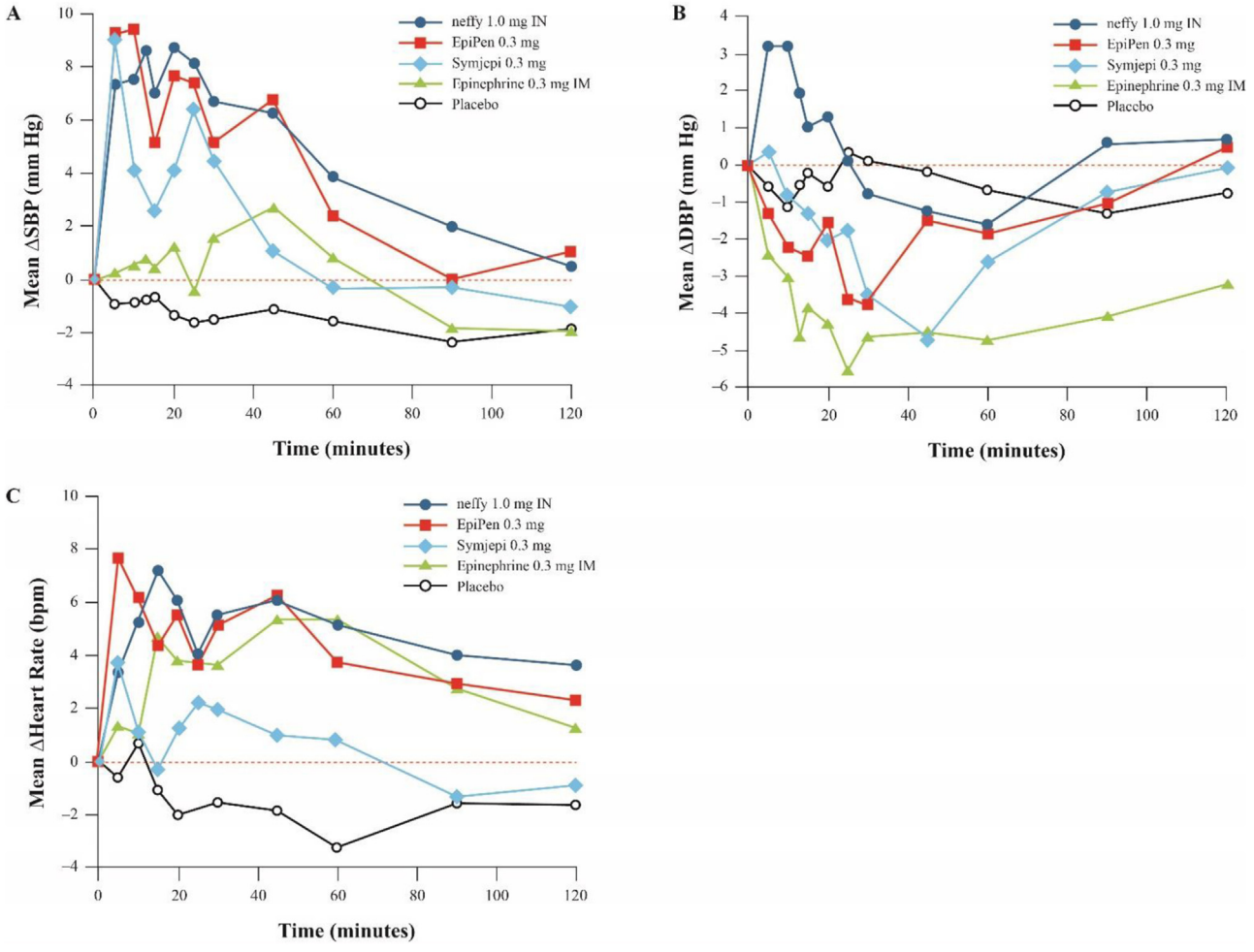

Figure 2. Pharmacodynamic measurements vs time after neffy, EpiPen, Symjepi, and Epinephrine 0.3 mg IM. (A) mean change from baseline in SBP, (B) mean change from baseline in DBP, and (C) mean change from baseline in heart rate. bpm, beats per minute; DBP, diastolic blood pressure; IM, intramuscular; IN, intranasal; SBP, systolic blood pressure.

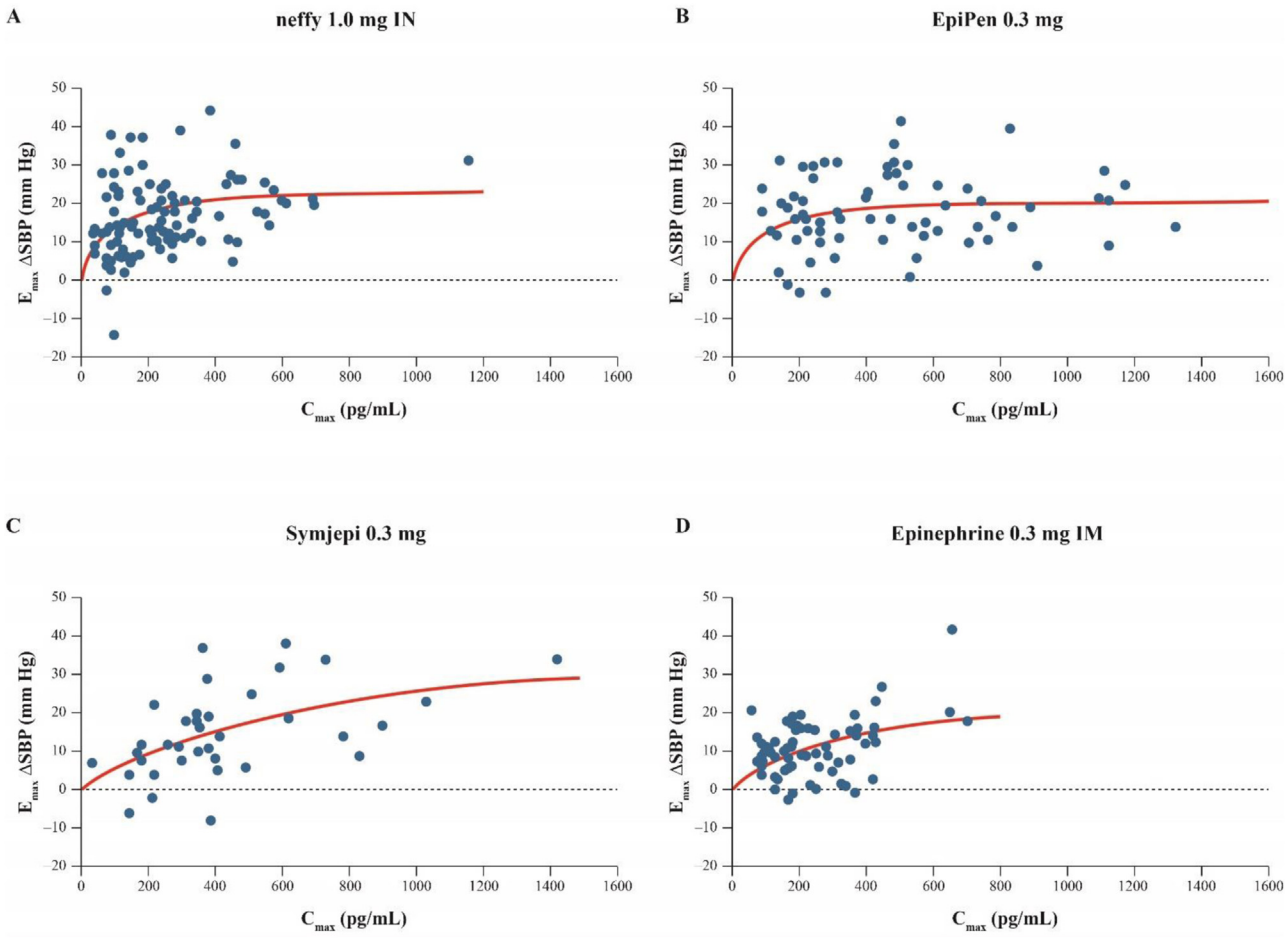

Figure 3. Relationship between change from baseline in SBP (E_{max}) and maximum plasma epinephrine concentration (C_{max}) after (A) neffy, (B) EpiPen, (C) Symjepi, and (D) Epinephrine 0.3 mg IM. C_{max}, maximum concentration; E_{max}, maximum effect; IM, intramuscular; IN, intranasal; SBP, systolic blood pressure.

discrepancy between the decrease in DBP after injection products in Figure 2 and the positive increase with respect to E_{max} is likely based on DBP vs time being means of at each time point whereas mean E_{max} is the mean of highest DBP change for each subject.

Heart Rate

The peak mean heart rate (HR) vs time was the greatest for EpiPen, followed by neffy, Epinephrine 0.3 mg IM, and Symjepi (Fig 2). The mean HR E_{max} values were similar among neffy (13.6 beats per minute [bpm]), EpiPen (14.4 bpm), and Epinephrine 0.3 mg IM (12.8 bpm). Symjepi resulted in a lower HR E_{max} (8.86 bpm) (Table 2). The longest TE_{max} was observed after Epinephrine 0.3 mg IM (30 minutes), followed by neffy (20 minutes), Symjepi (16 minutes), and EpiPen (14 minutes).

Pharmacokinetic-Pharmacodynamic Relationship

For both SBP and HR, there was a positive relationship between C_{max} and E_{max} (Figs. 3 and 4). It is also important to note that this relationship between C_{max} and E_{max} appeared to be limited to lower C_{max} levels. Once C_{max} levels reached approximately 500 pg/mL, additional increases in C_{max} did not translate into increases in E_{max}. This observation was noted across all treatments.

A similar pattern was observed when the change from baseline DBP E_{max} was plotted against C_{max} (Fig 5), with neffy more likely than were injection products to result in consistent increases in DBP.

Discussion

Several routes of epinephrine administration are currently approved for the treatment of severe allergic reactions including anaphylaxis, such as intravenous infusion, intravenous bolus, IM injection, and subcutaneous injection. In addition, multiple approved EAI devices are available for IM epinephrine delivery. Although recent studies have indicated that there are PK differences among injection products, very little is known about the PD differences. However, extensive clinical experience shows that all these routes of administration are safe and effective for the treatment of severe allergies, including anaphylaxis. Epinephrine is the first-line treatment for anaphylaxis, and even though its labeling in the United States allows its use as subcutaneous injection, current international guidelines specify that IM epinephrine injection is the preferred route of administration and recommend it for first-line treatment of severe allergic reactions and anaphylaxis.[4–6]

Epinephrine autoinjectors have long been considered clinically interchangeable. However, recent findings reveal meaningful PK differences between EAIs and manual epinephrine IM injection, and among the different EAI devices. The discovery of variable PK profiles among the currently approved epinephrine products challenges the assumption that these products can be considered clinically interchangeable.[6] The present analysis explored the PK and PD profiles of these routes of administration and found notable differences. Although neffy, EpiPen, and Symjepi showed comparable effects on the change from baseline in SBP and HR, neffy led to a modestly more robust increase in E_{max} for SBP, despite having lower or comparable C_{max} relative to injection products. This greater effect on SBP is likely

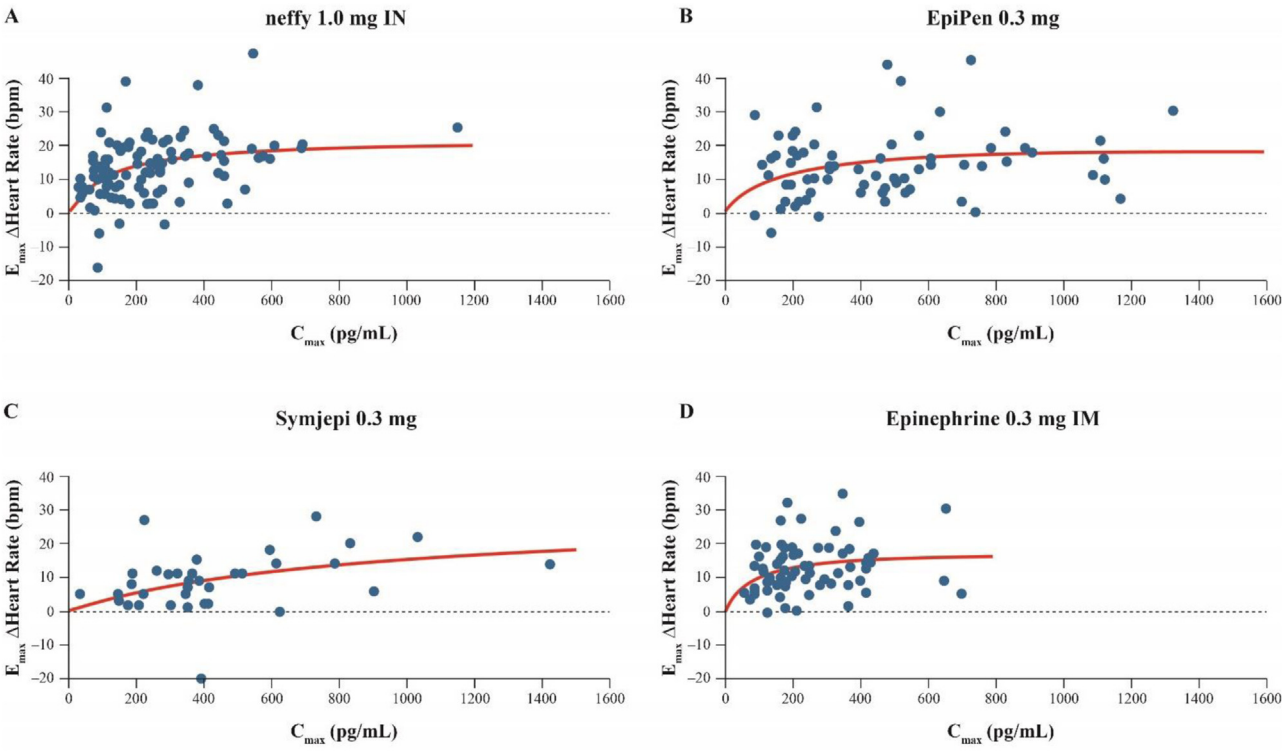

Figure 4. Relationship between change from baseline in heart rate (E_{max}) and maximum plasma epinephrine concentration (C_{max}) after (A) neffy, (B) EpiPen, (C) Symjepi, and (D) Epinephrine 0.3 mg IM. bpm, beats per minute; C_{max}, maximum concentration; E_{max}, maximum effect; IM, intramuscular; IN, intranasal.

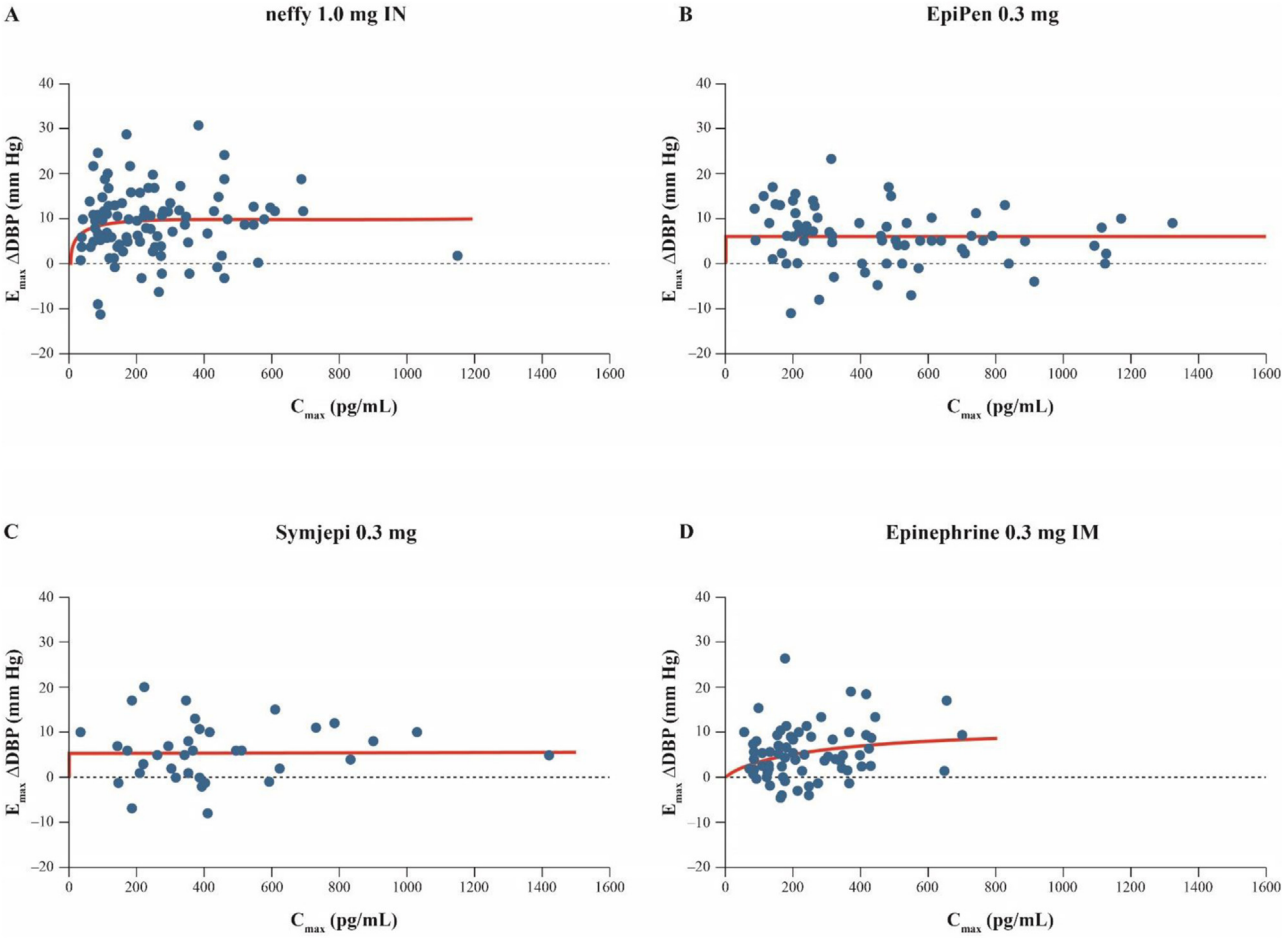

Figure 5. Relationship between change from baseline in diastolic blood pressure (E_{max}) and maximum plasma epinephrine concentration (C_{max}) after (A) neffy, (B) EpiPen, (C) Symjepi, and (D) Epinephrine 0.3 mg IM. C_{max}, maximum concentration; DBP, diastolic blood pressure; E_{max}, maximum effect, IM, intramuscular; IN, intranasal.

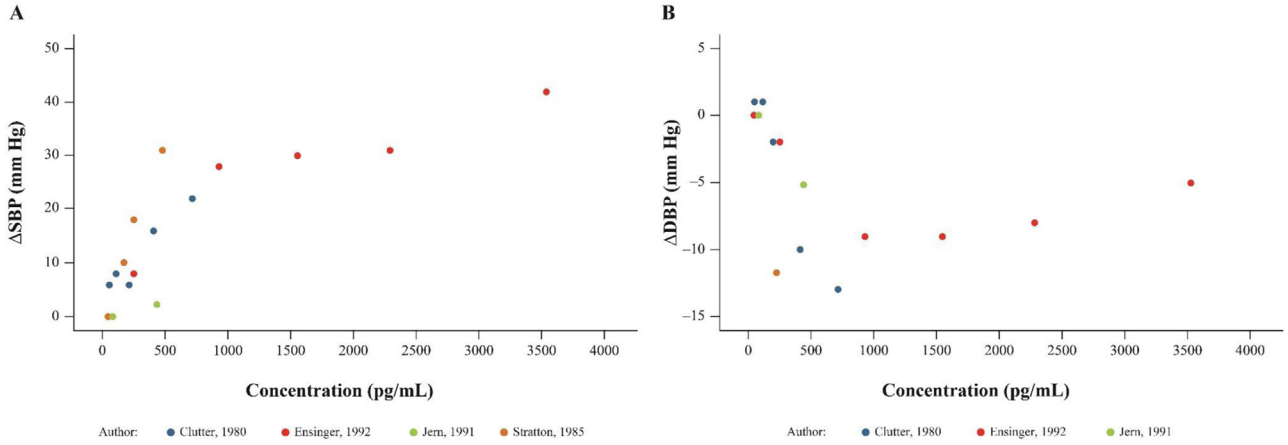

Figure 6. Relationship between systolic and diastolic blood pressure and epinephrine concentrations based on previous publications.[8–10,14] DBP, diastolic blood pressure; SBP, systolic blood pressure.

because of the difference in the DBP response between neffy and injection products, an observation that may be attributed to the differential affinities for the adrenergic receptor subtypes. Specifically, the β_2 receptors are in skeletal muscles and have a relatively high affinity for epinephrine, allowing them to be preferentially activated by direct IM injection of epinephrine (through either manual injection or autoinjector). Activation of the β_2 adrenergic receptors occurs at relatively low concentrations of epinephrine and promotes vasodilation in the skeletal muscle, causing a decrease in peripheral vascular resistance and increased blood flow to skeletal muscle, ultimately resulting in a decrease in DBP.[7] This β_2-mediated DBP-lowering effect persists until epinephrine concentrations increase to levels sufficient to activate the α_1 receptors responsible for vasoconstriction and increased vascular resistance, ultimately resulting in a net increase in both SBP and DBP.[7] Other studies based on intravenous epinephrine infusion also support this hypothesis,[8–10] as seen in the plot for mean DBP change vs epinephrine concentration (Fig 6), which shows a transient decrease in DBP at a lower epinephrine level followed by a subsequent gradual increase toward baseline as epinephrine levels increased.

It is also important to note that the decrease in DBP may also be driving an attenuation of the increase in SBP, one of the key mechanisms behind the ability of epinephrine to treat severe allergic reactions including anaphylaxis. When DBP decreases, venous return also decreases, followed by a decrease in cardiac output, which may decrease SBP. Therefore, decreases in DBP owing to β_2-mediated vasodilatation directly result in an initial decrease in SBP and/or mitigate the epinephrine-mediated increase in SBP.[1] In dog models of anaphylaxis, decreased cardiac output and stroke volume was observed with IM epinephrine injection compared with intravenous bolus and infusion of epinephrine.[11,12] This supports the suggestion that vasodilatation in the skeletal muscle affects cardiac output. The greater SBP response after intranasal neffy administration may therefore be attributed to bypassing the β_2-mediated vasodilatation in the skeletal muscle, which is particularly important during the treatment of anaphylaxis, when blood vessels are already dilated in response to the release of mediators including histamine.

In addition to the variable systolic and diastolic blood pressure responses resulting from different routes of administration, the observed PD differences among injection products may possibly be driven by both the variability of injection force and speed based on the devices.[1,3] EpiPen had the fastest C_{max} that resulted in the highest E_{max}. Epinephrine 0.3 mg IM had the slowest and lowest C_{max} that resulted in the lowest E_{max}, whereas the C_{max} and E_{max} values for Symjepi were between those for manual epinephrine IM injection and EpiPen.

Although the potential for severe cardiovascular adverse events when epinephrine is administered too quickly has been previously reported,[13] there appears to be a ceiling effect for SBP E_{max} when epinephrine is dosed at an appropriate speed, whereby maximum PD expression is achieved at epinephrine levels that are below the highest C_{max} levels. Thus, as reported previously, increase in C_{max} beyond approximately 500 pg/mL does not appear to result in additional corresponding increases in SBP. Scatter plots of mean SBP change vs epinephrine concentration based on intravenous epinephrine infusion indicate maximum increase in SBP at plasma concentrations of approximately 1000 pg/mL, and that further increase in plasma epinephrine levels did not translate into additional increases in SBP (Fig 6).[8,9,14] Similarly, Wortsman reported that all cardiac and metabolic epinephrine actions are fully expressed at concentrations of approximately 1000 pg/mL.[15] Although the present analysis was based on only single dose, a similar finding was observed after a twice-dosing protocol that included higher C_{max} levels.

The main limitation of this analysis is the small number of subjects in the Symjepi group, which may limit the generalizability of these observations. More studies are required to confirm these observations.

In conclusion, this analysis revealed PK and PD differences among intranasal and various IM injection methods. Intranasal administration of epinephrine through neffy resulted in comparable or higher PD responses relative to currently available delivery systems for epinephrine (EAIs and manual IM injection), despite having lower end of C_{max}. Regardless of route of administration, these data show that when administered intranasally or through IM injection, the maximum PD effects are subject to a ceiling effect.

Acknowledgments

Medical writing was provided by Tricia Bliven-Chasinoff, MS, of Pacific Link Consulting and was funded by ARS Pharmaceuticals.

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.anai.2022.10.024

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Supplementary Data

eTable 1
Baseline Demographics of Study Participants

Characteristic	Treatment				
	Neffy 1.0 mg IN n = 135	Epinephrine 0.3 mg IM n = 104	Symjepi 0.3 mg n = 36	EpiPen 0.3 mg n = 71	Placebo IM n = 70
Sex, n (%)					
Male	74 (54.8)	62 (59.6)	17 (47.2)	41 (57.7)	42 (60.0)
Female	61 (45.2)	42 (40.4)	19 (52.8)	30 (42.3)	28 (40.0)
Age, y mean (SD)	37.5 (9.55)	37.2 (9.99)	39.6 (8.51)	37.6 (9.52)	38.7 (9.98)
Height, cm mean (SD)	171 (9.81)	171 (9.39)	167 (10.5)	170 (9.89)	171 (8.95)
Weight, kg mean (SD)	75.7 (12.0)	7.5 (11.7)	72.2 (11.8)	74.6 (11.7)	76.5 (10.7)
BMI, kg/m^2 mean (SD)	25.9 (2.70)	25.9 (2.68)	25.7 (2.58)	25.7 (2.91)	26.2 (2.48)

Abbreviations: BMI, body mass index; IM, intramuscular; IN, intranasal.