Poster L20

5-Period, 5-Treatment Crossover Study to Compare the Pharmacokinetics of Intranasal and Intramuscular Epinephrine Administration in Healthy Adult Participants

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Presented at the American Academy of Allergy, Asthma & Immunology (AAAAI) National Conference, February 26–March 1, 2021, Virtual Annual Meeting

INTRODUCTION

- Epinephrine is the first-line therapy for anaphylaxis, commonly administered via intramuscular (IM) autoinjector injection[1]
- Patient adherence with autoinjector use may be compromised owing to patient lack of compliance to carry their autoinjectors with them routinely, reluctance to use self-injectors (eg, needle anxiety or fear) or application error (eg, lack of training, injection injuries)[1–5]
- Delayed epinephrine administration or exposure during anaphylactic events may increase risk of hospitalizations and potentially fatal outcomes[6]
- Intranasal (IN) administration has been considered for drugs requiring rapid onset of action, such as those for opioid overdose reversal, and has been explored for anaphylaxis treatment[7–10]
- The IN route is a potential alternative for the treatment of patients experiencing an anaphylactic event[7]

AIMS

- Compare the dose ranging pharmacokinetic (PK) and pharmacodynamic (PD) effects of IN nasal spray epinephrine versus IM autoinjector epinephrine in healthy participants

METHODS

Study participants

- Healthy male and female participants were enrolled in the study (19–45 years of age with body mass index ≥18 and ≤32 kg/m^2)
- Written informed consent was obtained from all participants
- Exclusion criteria included a history or presence of clinically significant medical conditions, including heart disease, asthma, severe allergic reactions, and food allergies, as well as any signs of respiratory tract infection within 6 weeks of screening

Study design

- This was an open-label, randomized, 5-treatment, 5-way crossover study
- Epinephrine administrations were as follows:
  - 6.6 mg IN via nasal spray (1 x 6.6 mg)
  - 4.4 mg IN via nasal spray (2 x 2.2 mg, opposite nostrils)
  - 8.8 mg IN via nasal spray (2 x 4.4 mg, opposite nostrils)
  - 13.2 mg IN via nasal spray (2 x 6.6 mg, opposite nostrils)
  - 0.3 mg IM via autoinjector (1 x 0.3 mg)
- Participants were randomized to one of five treatment sequences; epinephrine IN via nasal spray or IM via autoinjector was administered on Day 1 of each period
  - As needed for specific treatment groups, the second IN dose was administered within seconds after the first dose and to the opposite nostril
- There was a washout period of ≥1 day between doses

PK

- Blood samples were collected to measure plasma epinephrine concentrations at specified timepoints (–30, –20, –10, 1, 3, 5, 7, 10, 15, 20, 25, 30, 45, 60, 90, 120, 180, 360 minutes)
- PK parameters included the maximum observed concentration (C_{max}), C_{max} from time 0 to 10 minutes ($C_{max(10\ min)}$), time to reach C_{max} (T_{max}), and area under the plasma concentration–time curve (AUC) from time 0 to the 10-, 20-, 30-, 60-, and 360-minute postdose timepoints (AUC_{0-10}, AUC_{0-20}, AUC_{0-30}, AUC_{0-60}, AUC_{0-360})
- The proportion of participants within each treatment group achieving a target threshold epinephrine plasma concentration (100 and 200 pg/mL) within specified timepoints (10-, 20-, and 30- minutes post dose) was evaluated

PD

- Cardiovascular effects (heart rate and blood pressure) were measured at specified timepoints (–30, –20, –10, 1, 3, 5, 7, 10, 15, 20, 25, 30, 45, 60, 90, 120, 180, and 360 minutes)
- The PD parameter evaluated for heart rate was the maximum positive effect concentration (E_{max})

Safety

- Adverse events (AEs) were monitored and characterized by the Medical Dictionary for Regulatory Activities® (version 23.0)

Statistical analysis

- A noncompartmental approach was used to analyze individual plasma baseline-corrected epinephrine concentration–time data, as well as heart rate and blood pressure after each treatment using Phoenix WinNonlin® Version 8.1 and SAS® Version 9.4
- An analysis of variance was performed on the baseline-corrected, natural logarithm-transformed PK parameters
  - Participants in the PK population with insufficient data to calculate the PK parameters were included in concentration tables but excluded from summary statistics
- E_{max} descriptive statistics were generated using SAS® Version 9.4
- For baseline-corrected parameters, three predose values (epinephrine concentrations for PK, heart rate, and blood pressure measurements) were averaged (mean baseline) and subtracted from plasma epinephrine concentrations. Negative corrected concentrations were set to zero

RESULTS

- A total of 25 participants enrolled in the study; all 25 completed the study
- Overall, the mean ± standard deviation for participant age was 32 ± 6 years, and most participants were male (60%) and white (52%) (**Table 1**)
- The results for the comparison of interest (epinephrine 6.6 mg IN vs 0.3 mg IM groups) are reported in text, and results from all doses are shown in tables and figures

Table 1. Demographics and Baseline Characteristics

Characteristic	Overall N=25
Age (years)	32 ± 6
Male, n (%)	15 (60)
Race, n (%)	
White	13 (52)
Black	7 (28)
White, Asian	2 (8)
American Indian or Alaska Native	1 (4)
Asian	1 (4)
White, American Indian/Alaska Native	1 (4)
Weight (kg)	80 ± 18
Height (cm)	175 ± 10
BMI (kg/m^2)	26 ± 4

Results are reported as mean ± SD, unless noted otherwise.
BMI, body mass index; SD, standard deviation.

PK

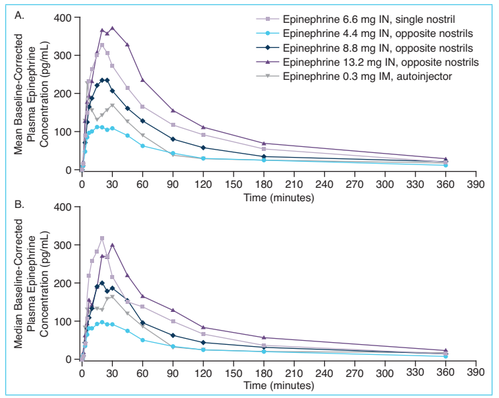
- Mean epinephrine exposure was greater after epinephrine 6.6 mg IN versus 0.3 mg IM (mean ± standard error, AUC_{0-10}, 1469 ± 226 vs 1430 ± 232 min*pg/mL; AUC_{0-20}, 4427 ± 622 vs 2825 ± 346 min*pg/mL; AUC_{0-30}, 7469 ± 1033 vs 4384 ± 457 min*pg/mL; AUC_{0-60}, 14,000 ± 1994 vs 8225 ± 707 min*pg/mL; AUC_{0-360}, 33,680 ± 4631 vs 16,550 ± 1285 min*pg/mL) (**Table 2; Figure 1A**)
- Median epinephrine exposure was greater after epinephrine 6.6 mg IN versus 0.3 mg IM (**Figure 1B**)
- Mean C_{max} values were greater after epinephrine 6.6 mg IN versus 0.3 mg IM (mean [percent coefficient of variation], C_{max}, 397 [68] vs 288 [68] pg/mL; $C_{max(10\ min)}$, 277 [69] vs 246 [86] pg/mL) (**Table 2**)
- In bioavailability assessments of epinephrine 6.6 mg IN and 0.3 mg IM, the geometric mean ratios (90% confidence interval [CI]) for C_{max} and AUC_{0-360} were 123% (94–161) and 168% (134–211), respectively (**Table 3**)
- After 20 minutes, baseline-corrected epinephrine concentrations ≥100 pg/mL were reached by 80% of participants after both epinephrine 6.6 mg IN and 0.3 mg IM (**Figure 2A**); epinephrine concentrations ≥200 pg/mL were reached by 60% and 56% of participants after epinephrine 6.6 mg IN and 0.3 mg IM, respectively (**Figure 2B**)

Table 2. Baseline-Corrected Plasma Epinephrine PK After Epinephrine IN Via Nasal Spray Versus IM Via Autoinjector

PK parameter	6.6 mg IN N=25	4.4 mg IN N=25	8.8 mg IN N=25	13.2 mg IN N=25	0.3 mg IM N=25
C_{max} (pg/mL), mean (CV%)	397 (68)	166 (57)	311 (64)	490 (65)	288 (68)
$C_{max\ (10\ min)}$ (pg/mL), mean (CV%)	277 (69)	120 (81)	212 (79)	272 (81)	246 (86)
T_{max} (min), median (minimum, maximum)	20 (5, 62)	20 (5, 410)	20 (5, 180)	30 (3, 60)	10 (5, 90)
AUC_{0-10} (min*pg/mL)					
Mean ± SE	1469 ± 226	665 ± 106	1096 ± 179	1454 ± 271	1430 ± 232
Geometric mean (CV%)	936 (177)	464 (119)	699 (149)	1050 (94)	979 (126)
AUC_{0-20} (min*pg/mL)					
Mean ± SE	4427 ± 622	1754 ± 228	3243 ± 507	4452 ± 687	2825 ± 346
Geometric mean (CV%)	3054 (133)	1395 (84)	2230 (126)	3393 (88)	2273 (84)
AUC_{0-30} (min*pg/mL)					
Mean ± SE	7469 ± 1033	2828 ± 351	5537 ± 870	8072 ± 1240	4384 ± 457
Geometric mean (CV%)	5291 (122)	2323 (75)	3851 (120)	6183 (87)	3756 (67)
AUC_{0-60} (min*pg/mL)					
Mean ± SE	14,000 ± 1994	5482 ± 674	10,470 ± 1525	17,590 ± 2662	8225 ± 707
Geometric mean (CV%)	10,170 (110)	4615 (67)	7825 (99)	14150 (73)	7433 (51)
AUC_{0-360} (min*pg/mL)					
Mean ± SE	33,680 ± 4631[a]	13,410 ± 1557[a]	24,120 ± 2800[a]	41,870 ± 5430	16,550 ± 1285
Geometric mean (CV%)	26,370 (88)[a]	11,660 (58)[a]	20,440 (68)[a]	35,320 (64)	15,160 (48)

[a]n=24.
AUC_{0-10}, AUC from time 0 to the 10-minute postdose timepoint; AUC_{0-20}, AUC from time 0 to the 20-minute postdose timepoint; AUC_{0-30}, AUC from time 0 to the 30-minute postdose timepoint; AUC_{0-60}, AUC from time 0 to the 60-minute postdose timepoint; AUC_{0-360}, AUC from time 0 to the 360-minute postdose timepoint; C_{max}, maximum observed concentration; $C_{max(10\ min)}$, maximum observed concentration from 0 to 10 minutes; CV, coefficient of variation, IM, intramuscular; IN, intranasal; SE, standard error; T_{max}, time to reach maximum concentration.

Figure 1. Mean (A) and Median (B) Baseline-Corrected Plasma Epinephrine Concentration-Time Profiles After Epinephrine IN Via Nasal Spray Versus IM Via Autoinjector



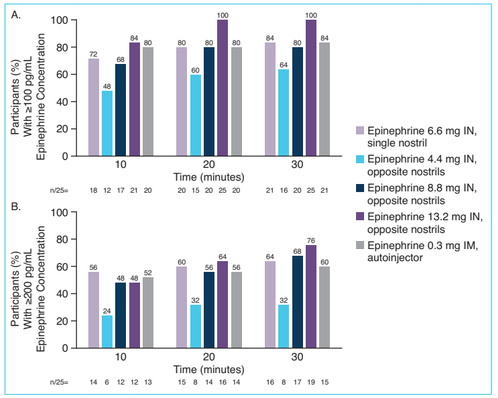
IM, intramuscular; IN, intranasal.

Table 3. Comparisons of Baseline-Corrected Plasma Epinephrine PK Parameters After Epinephrine 6.6 mg IN Via Nasal Spray Versus 0.3 mg IM Via Autoinjector

PK Parameter	Treatment: 6.6 mg IN N=25 Geometric LSM	Treatment: 0.3 mg IM N=25 Geometric LSM	Geometric mean ratio (%)	90% CIs	Intrasubject CV%
C_{max} (pg/mL)	293	238	123	94–161	61
AUC_{0-10} (min*pg/mL)	936	979	96	68–135	84
AUC_{0-20} (min*pg/mL)	3054	2273	134	101–179	67
AUC_{0-30} (min*pg/mL)	5291	3756	141	107–185	64
AUC_{0-60} (min*pg/mL)	10,170	7433	137	108–174	55
AUC_{0-360} (min*pg/mL)	25,460[a]	15,160	168	134–211	50

[a]n=24.
AUC_{0-10}, AUC from time 0 to the 10-minute postdose timepoint; AUC_{0-20}, AUC from time 0 to the 20-minute postdose timepoint; AUC_{0-30}, AUC from time 0 to the 30-minute postdose timepoint; AUC_{0-60}, AUC from time 0 to the 60-minute postdose timepoint; AUC_{0-360}, AUC from time 0 to the 360-minute postdose timepoint; CI, confidence interval; C_{max}, maximum observed concentration; CV, coefficient of variation; IM, intramuscular; IN, intranasal; LSM, least squares mean; PK, pharmacokinetic.

Figure 2. Proportion of Participants with Plasma Epinephrine Concentrations of ≥100 pg/mL (A) or ≥200 pg/mL (B) After Epinephrine IN Via Nasal Spray Versus IM Via Autoinjector

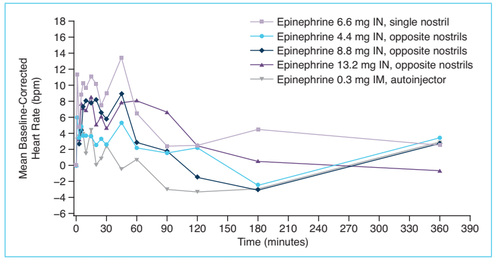


IM, intramuscular; IN, intranasal.

PD

- E_{max} least squares mean (LSM) values for baseline-corrected heart rate were 33 beats per minute (bpm) with epinephrine 6.6 mg IN versus 20 bpm with epinephrine 0.3 mg IM (LSM difference [90% CI], 13 [6, 19]), indicating a possible treatment effect
- Mean heart rate values were greater through 180 minutes after epinephrine 6.6 mg IN versus 0.3 mg IM (**Figure 3**)
- E_{max} of baseline-corrected systolic and diastolic blood pressure did not differ significantly with epinephrine 6.6 mg IN versus 0.3 mg IM

Figure 3. Mean Baseline-Corrected Heart Rate–Time Profiles After Epinephrine IN Via Nasal Spray Versus IM Via Autoinjector



bpm, beats per minute; IM, intramuscular; IN, intranasal.

Safety

- The percentage of participants with treatment-emergent AEs ranged from 44% (11/25) to 52% (13/25) in the IN groups and was 28% (7/25) in the IM group; all were transient and generally mild, and most resolved within minutes to hours (**Table 4**)
- Treatment-emergent AEs reported by ≥10% of participants per group included tremor, nausea, headache, palpitations, upper abdominal pain, and nasal discomfort (**Table 4**)
- There were no deaths, serious AEs, or participant discontinuations due to AEs

Table 4. Treatment-Emergent Adverse Events Occurring in ≥10% of Participants Receiving Epinephrine IN Via Nasal Spray or IM Via Autoinjector[a]

TEAEs, n (%)	6.6 mg IN N=25	4.4 mg IN N=25	8.8 mg IN N=25	13.2 mg IN N=25	0.3 mg IM N=25
Total	12 (48)	11 (44)	13 (52)	13 (52)	7 (28)
Tremor	4 (16)	1 (4)	3 (12)	5 (20)	2 (8)
Nausea	4 (16)	0	6 (24)	3 (12)	0
Headache	3 (12)	2 (8)	2 (8)	3 (12)	2 (8)
Palpitations	3 (12)	1 (4)	0	0	0
Abdominal pain, upper	2 (8)	0	2 (8)	4 (16)	0
Nasal discomfort	1 (4)	3 (12)	2 (8)	0	0

[a]If a participant had two or more clinical AEs, the participant was counted only once within a category.
AE, adverse event; IM, intramuscular; IN, intranasal; TEAEs, treatment-emergent adverse events.

CONCLUSIONS

1. **The single epinephrine 6.6 mg IN dose had a favorable release profile compared with a single 0.3 mg IM injection via autoinjector in total epinephrine exposure and epinephrine bioavailability**
2. **Although not clinically meaningful, mean heart rate was generally greater with IN nasal spray versus IM autoinjector epinephrine. Also, any changes in blood pressure were not clinically meaningful after epinephrine 6.6 mg IN versus 0.3 mg IM**
3. **Epinephrine IN via nasal spray was generally safe and well tolerated**
4. **Epinephrine IN via bidose nasal spray is a potential novel therapeutic option in the treatment of patients experiencing anaphylactic events; these data suggest that the bidose nasal spray may produce a more favorable epinephrine exposure profile and alleviation of anaphylactic symptoms as compared with the autoinjector**

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Acknowledgments and Disclosures

This research was supported by Bryn Pharma, LLC. Medical writing assistance was provided by Caryne Craige, PhD, of Fishawack Communications Inc., part of Fishawack Health; funding for this assistance was provided by Bryn Pharma, LLC.

David Dworaczyk, PhD, is an employee of Bryn Pharma, LLC. Allen Hunt, MD, is an employee of Celerion and received funding support from Bryn Pharma, LLC, to conduct this research study.