Poster L34

Pharmacokinetic and Pharmacodynamic Effects of Intranasal Epinephrine Versus Intramuscular Epinephrine in Adults

David Dworaczyk, PhD,[1] and Allen Hunt, MD[2]

[1]Bryn Pharma, LLC, Raleigh, NC, USA;
[2]Celerion, Lincoln, NE, USA

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INTRODUCTION

- Epinephrine is the first-line therapy for anaphylaxis, commonly administered via autoinjector intramuscular (IM) injection[1]
- Patient concerns with autoinjectors (injuries, epinephrine expiration, and anxiety with use) may interfere with compliance and epinephrine administration during anaphylaxis[1,2]
- Delayed epinephrine treatment in anaphylaxis may increase the risk of hospitalizations and potentially fatal outcomes[3]
- IN administration is an approved approach for conditions like opioid overdose reversal, and has been explored for anaphylaxis treatment[4–6]
- The IN route is a potential alternative for anaphylaxis treatment

AIMS

- Compare pharmacokinetics (PK) and pharmacodynamics of epinephrine IN versus IM

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 respiratory tract infection, asthma, severe allergic reactions, and foot allergies

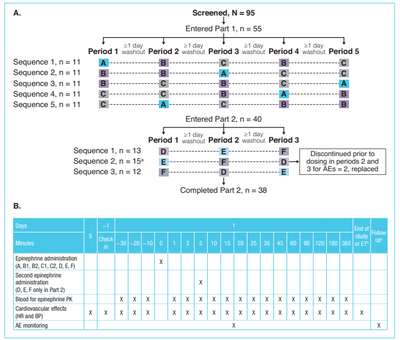
Study design

- This was an open-label, 2-part comparative bioavailability study to compare PK and pharmacodynamics after epinephrine IN or IM
- Part 1 was conducted as a randomized, 3-treatment, 5-period, semi-replicate design (**Figure 1A**)
  - Participants received a single administration of each per period:
    - A: Epinephrine 6.6 mg IN via nasal spray
      - Participants were instructed to breathe normally through their mouth during IN administration
    - B: Epinephrine 0.3 mg IM via EpiPen® (Mylan Specialty LP, Canonsburg, PA)
    - C: Epinephrine 0.5 mg IM via manual syringe
- Part 2 was a randomized, 3-treatment, 3-period crossover design conducted in parallel with part 1 (**Figure 1A**)
  - Participants received treatments twice ("2 x") 5 minutes apart per period:
    - D: Epinephrine 2 x 6.6 mg IN in opposite nostrils
    - E: Epinephrine 2 x 6.6 mg IN in the same nostril
    - F: Epinephrine 2 x 0.3 mg IM in opposite thighs

PK

- Blood samples were collected at specified times to measure plasma epinephrine (**Figure 1B**)
- PK parameters included maximum observed concentration (C_{max}), time to reach C_{max} (T_{max}), area under the plasma concentration-time curve (AUC) from time 0 to the 20-minute postdose time point (AUC_{0-20}), and AUC from time 0 to the 360-minute postdose time point (AUC_{0-360})

Figure 1. Participant Disposition (A) and Study Design (B)



[a]One participant who was randomized to treatment sequence EFD was dosed as DFE in error.
[b]Performed at end of part 1 and part 2 or prior to early termination from study.
[c]The clinical research unit followed up approximately 7 days after the last study drug administration for information on AEs.
A, epinephrine 6.6 mg IN; AE, adverse event; B1, epinephrine 0.3 mg IM via EpiPen® first administration; B2, epinephrine 0.3 mg IM via EpiPen second administration; BP, blood pressure; C1, epinephrine 0.5 mg IM via manual syringe first administration; C2, epinephrine 0.5 mg IM via manual syringe second administration; ET, early termination; HR, heart rate; PK, pharmacokinetics; S, screening.

Pharmacodynamics

- Cardiovascular effects (heart rate and blood pressure) were assessed at specified times (**Figure 1B**)

Post hoc analyses

- Post hoc analyses compared bioavailability after B (epinephrine 0.3 mg IM) in part 1 with D (epinephrine 2 x 6.6 mg IN, opposite nostrils) and E (epinephrine 2 x 6.6 mg IN, same nostril) in part 2
- Post hoc analyses calculated the percentage of participants with plasma epinephrine concentrations of 100 or 200 pg/mL

Safety

- Adverse events (AEs) were monitored and characterized by the Medical Dictionary for Regulatory Activities® (version 22.0)

Statistical analysis: PK

- PK data were analyzed using a noncompartmental approach with Phoenix® WinNonlin® version 7.0 and SAS® version 9.4
- AUC_{0-20} and AUC_{0-360} values were estimated by interpolation or extrapolation
- T_{max} values were analyzed using nonparametric analysis for paired samples
- In post hoc analyses of bioequivalence, the 80% to 125% limit for 90% confidence interval (CI) was used for geometric mean ratios (GMR)
- Baseline-corrected, log-transformed PK parameters were analyzed by a generalized linear model and analysis of variance (ANOVA)
- Baseline-corrected heart rate and blood pressure measurements for maximum positive effect concentration (E_{max}) were analyzed by SAS version 9.4 and ANOVA

RESULTS

- Out of 95 total participants, 55 enrolled in part 1 and 40 enrolled in part 2 (**Figure 1A**)
- Of those, 2 participants voluntarily withdrew from part 2
- In part 1, the average participant age was 33 ± 6 years. In part 2, the average age was 31 ± 7 years (**Table 1**)

Table 1. Demographics and Baseline Characteristics for Overall Populations in Part 1 and Part 2

Characteristic	Part 1 N = 55	Part 2 N = 40
Age (years), mean ± SD	33 ± 6	31 ± 7
Male, n (%)	44 (80%)	31 (78%)
Weight (kg), mean ± SD	83 ± 14	77 ± 13
Height (cm), mean ± SD	177 ± 9	174 ± 8
BMI (kg/m^2), mean ± SD	26 ± 3	25 ± 3

SD, standard deviation.

PK

- Double epinephrine IN (D, epinephrine 2 x 6.6 mg IN, opposite nostrils and E, epinephrine 2 x 6.6 mg IN, same nostril) resulted in greater C_{max} and AUC_{0-20} than single epinephrine IM (B pooled, 0.3 mg IM) (C_{max}, 644 ± 853 and 1237 ± 2099 vs 374 ± 503 pg/mL and AUC_{0-20}, 6367 ± 9666 and 13,380 ± 21,134 vs 3263 ± 2631 min*pg/mL) (**Table 2**)
- Single epinephrine IN (A, epinephrine 6.6 mg IN) resulted in lower epinephrine exposure than single epinephrine IM (B, 0.3 mg IM and C, 0.5 mg IM) (**Table 2** and **Figure 2A**)
- Double epinephrine IN (E, epinephrine 2 x 6.6 mg IN, same nostril) resulted in greater exposure than double epinephrine IM (F, 2 x 0.3 mg IM) (**Table 2** and **Figure 2B**)
- In bioavailability assessments of treatments D (epinephrine 2 x 6.6 mg IN, opposite nostrils) and B (B1 and B2 pooled, 0.3 mg IM), the GMRs (90% CI) for C_{max} and AUC_{0-360} were 145 (114–185) and 222 (184–267), respectively (**Table 3**)
- For treatments E (epinephrine 2 x 6.6 mg IN, same nostril) and B (B1 and B2 pooled, 0.3 mg IM), GMRs (90% CI) for C_{max} and AUC_{0-360} were 265 (209–337) and 322 (274–379), respectively (**Table 3**)
- A greater percentage of participants achieved epinephrine concentrations of 100 and 200 pg/mL after treatment E (epinephrine 2 x 6.6 mg IN, same nostril) in part 2 compared with treatment B (B1 and B2 pooled, 0.3 mg IM) in part 1, except at 60 minutes, when the percentage achieving 100 pg/mL was the same (**Table 4**)

Pharmacodynamics

- There were no differences in average E_{max} for heart rate among groups in part 1 (mean ± SD E_{max}, A [epinephrine 6.6 mg IN]: 24 ± 15; B1 [epinephrine 0.3 mg IM]: 23 ± 12; B2 [epinephrine 0.3 mg IM]: 23 ± 14; C1 [epinephrine 0.5 mg IM]: 25 ± 14; C2 [epinephrine 0.5 mg IM]: 25 ± 18 beats per minute (bpm)
- There were no differences in mean heart rate among groups in part 1 (**Figure 3A**)
- In part 2, mean heart rate was slightly increased after E (epinephrine 2 x 6.6 mg IN, same nostril) compared with D (2 x 6.6 mg IN, opposite nostrils) or F (0.3 mg IM, opposite thighs) (**Figure 3B**)
- There were no differences in mean systolic blood pressure in part 1 or 2 (**Figure 4**)

Safety

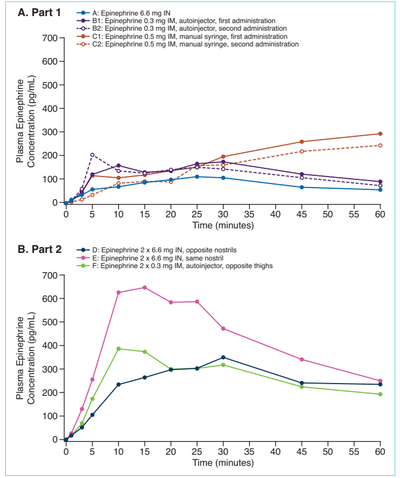
- The most common AE reported after IN epinephrine was nasal discomfort. The most common AEs after IM epinephrine were pain in extremity with B1, B2, C1, and C2 (epinephrine 0.3 mg and 0.5 mg IM) and tremor with F (2 x 0.3 mg IM) (**Table 5**)

Table 2. Baseline-Corrected Plasma Epinephrine PK after Epinephrine IN or IM

	Part 1							Part 2		
PK parameter	A 6.6 mg IN n = 55	B1 0.3 mg IM, first administration n = 55	B2 0.3 mg IM, second administration n = 55	B, pooled n = 110	C1 0.5 mg IM, first administration n = 55	C2 0.5 mg IM, second administration n = 55	C, pooled n = 110	D 2 x 6.6 mg IN, opposite nostrils n = 38	E 2 x 6.6 mg IN, same nostril n = 40	F 2 x 0.3 mg IM, opposite thighs n = 39
C_{max} (pg/mL), mean ± SD	193 ± 139	308 ± 152	440 ± 692	374 ± 503	712 ± 2468	351 ± 206	532 ± 1753	644 ± 853	1237 ± 2099	758 ± 626
T_{max} (min), median (minimum, maximum)	25 (2, 122)	16 (2, 60)	10 (1, 61)	15 (1, 61)	46 (3, 91)	45 (5, 120)	46 (3, 120)	25 (3, 61)	16 (3, 91)	15 (3, 45)
AUC_{0-20} (min*pg/mL), mean ± SD	1804 ± 1369	2898 ± 1808	3628 ± 3229	3263 ± 2631	3832 ± 9114	1777 ± 1544	2804 ± 6587	6367 ± 9666	13,380 ± 21,134	7993 ± 7771
AUC_{0-360} (min*pg/mL), mean ± SD	18,970 ± 21,708[a]	17,980 ± 5698[b]	18,470 ± 7761[c]	18,230 ± 6799	35,170 ± 12,887	30,880 ± 9467	33,020 ± 11,460	47,940 ± 38,481[d]	64,380 ± 40,957[e]	39,080 ± 18,710

[a]n=49; [b]n=50; [c]n=52; [d]n=36; [e]n=38.
AUC_{0-20}, area under the plasma concentration-time curve from time 0 to the 20-minute postdose time point; AUC_{0-360}, AUC from time 0 to the 360-minute postdose time point; C_{max}, maximum observed concentration; IM, intramuscular; IN, intranasal; SD, standard deviation; T_{max}, time to reach maximum concentration.

Figure 2. Median Baseline-Corrected Plasma Concentration–Time Profiles After Epinephrine IN or IM in Part 1 (A) and Part 2 (B)



IM, intramuscular; IN, intranasal.

Table 3. Comparisons of Baseline-Corrected Plasma Epinephrine PK Parameters After 2 Epinephrine 6.6 mg IN (Opposite or Same Nostrils) Administrations Versus 1 Epinephrine 0.3 mg IM Administration

	Treatment				
	D 2 x 6.6 mg IN, opposite nostrils	B 0.3 mg IM	Geometric mean ratio	90% confidence intervals	Intra-subject CV%
C_{max} GLSM, pg/mL	n = 38 412	n = 110 284	145	114–185	71
AUC_{0-360} GLSM, min*pg/mL	n = 36 37,380	n = 102 16,850	222	184–267	27
	Treatment				
	E 2 x 6.6 mg IN, same nostril	B 0.3 mg IM	Geometric mean ratio	90% confidence intervals	Intra-subject CV%
C_{max} GLSM, pg/mL	n = 40 752	n = 110 284	265	209–337	71
AUC_{0-360} GLSM, min*pg/mL	n = 38 54,300	n = 102 16,860	322	274–379	27

AUC_{0-360}, area under the plasma concentration-time curve from time 0 to the 360-minute postdose time point; C_{max}, maximum observed concentration; CV, coefficient of variation; GLSM, geometric least squares mean; IM, intramuscular; IN, intranasal; PK, pharmacokinetic.

Table 4. Percentage of Participants Who Reached Plasma Epinephrine Concentrations of 100 or 200 pg/mL

Threshold (pg/mL)	Time point (mins)	Part 1			Part 2	
		B1 0.3 mg IM, first administration n = 55, n (%)	B2 0.3 mg IM, second administration n = 55, n (%)	B, pooled n = 110	D 2 x 6.6 mg IN, opposite nostrils n = 38, n (%)	E 2 x 6.6 mg IN, same nostril n = 40, n (%)
100	10	41 (75)	41 (75)	82 (75)	33 (87)	33 (83)
	20	46 (84)	45 (82)	91 (83)	35 (92)	36 (90)
	30	50 (91)	50 (91)	100 (91)	36 (95)	38 (95)
	60	53 (96)	51 (93)	104 (95)	36 (95)	38 (95)
200	10	26 (47)	33 (60)	59 (54)	21 (55)	30 (75)
	20	31 (56)	35 (64)	66 (60)	27 (71)	33 (83)
	30	39 (71)	37 (67)	76 (69)	28 (74)	37 (93)
	60	40 (73)	39 (71)	79 (72)	28 (74)	38 (95)

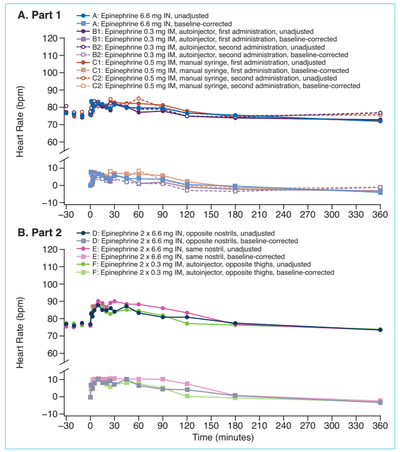
IM, intramuscular; IN, intranasal.

Table 5. Safety and Common Adverse Events in ≥10% of Participants per Period

	Part 1					Part 2		
Adverse event, n (%)	A 6.6 mg IN n = 55	B1 0.3 mg IM, first administration n = 55	B2 0.3 mg IM, second administration n = 55	C1 0.5 mg IM, first administration n = 55	C2 0.5 mg IM, second administration n = 55	D 2 x 6.6 mg IN, opposite nostrils n = 38	E 2 x 6.6 mg IN, same nostril n = 40	F 2 x 0.3 mg IM, opposite thigh n = 39
Nasal discomfort	5 (9)	0	0	0	0	7 (18)	9 (23)	1 (3)
Headache	4 (7)	2 (4)	1 (2)	3 (5)	1 (2)	2 (5)	5 (13)	2 (5)
Abdominal pain upper	2 (4)	0	0	0	0	4 (11)	4 (10)	0
Nausea	2 (4)	0	0	0	0	2 (5)	4 (10)	0
Rhinorrhea	1 (2)	0	1 (2)	0	0	5 (13)	1 (3)	2 (5)
Tremor	0	2 (4)	1 (2)	1 (2)	1 (2)	5 (13)	6 (15)	4 (10)
Pain in extremity	0	4 (7)	5 (9)	7 (13)	5 (9)	0	0	3 (8)

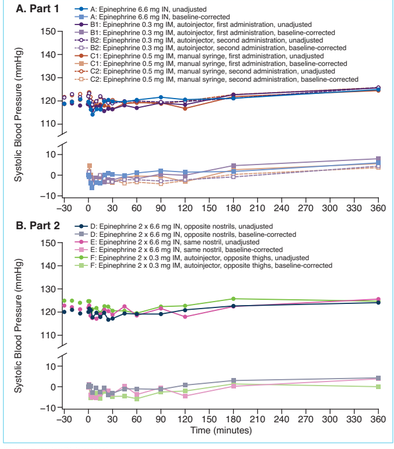
IM, intramuscular; IN, intranasal.

Figure 3. Unadjusted and Baseline-Corrected Mean Heart Rate–Time Profiles After Epinephrine IN or IM in Part 1 (A) and Part 2 (B)



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

Figure 4. Unadjusted and Baseline-Corrected Mean Systolic Blood Pressure–Time Profiles After Epinephrine IN or IM in Part 1 (A) and Part 2 (B)



IM, intramuscular; IN, intranasal.

CONCLUSIONS

1. Two epinephrine doses in the same nostril led to increased epinephrine absorption versus 2 IN doses in opposite nostrils and 2 IM doses; 2 epinephrine doses in the same or opposite nostrils led to substantially greater epinephrine absorption vs 1 epinephrine IM dose
2. At most times points, a greater percentage of participants reached epinephrine 100 and 200 pg/mL after epinephrine IN vs IM
3. There were no clinically significant differences in heart rate or blood pressure after epinephrine IN or IM
4. Epinephrine IN was safe and well-tolerated
5. IN epinephrine via bidose nasal spray is a potential novel therapeutic option in anaphylaxis treatment, which allows patients to administer a second dose readily if the first dose does not abate symptoms

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