Cardiovascular Safety of Intramuscular and Intranasal Epinephrine Administration

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RATIONALE

- Systolic blood pressure (SBP) and heart rate (HR) are generally thought to have linear relationships with plasma epinephrine concentrations, an understanding based on continuous infusion studies, where epinephrine was increased slowly.
- However, the relation of epinephrine concentrations to SBP and HR following acute administration (i.e., intramuscular [IM] injection) is unclear.
- Given that epinephrine administration may result in high epinephrine concentrations, it is important to characterize the pharmacokinetic and pharmacodynamic relationship for different routes of administration.

METHODS

STUDY DESIGN AND POPULATION

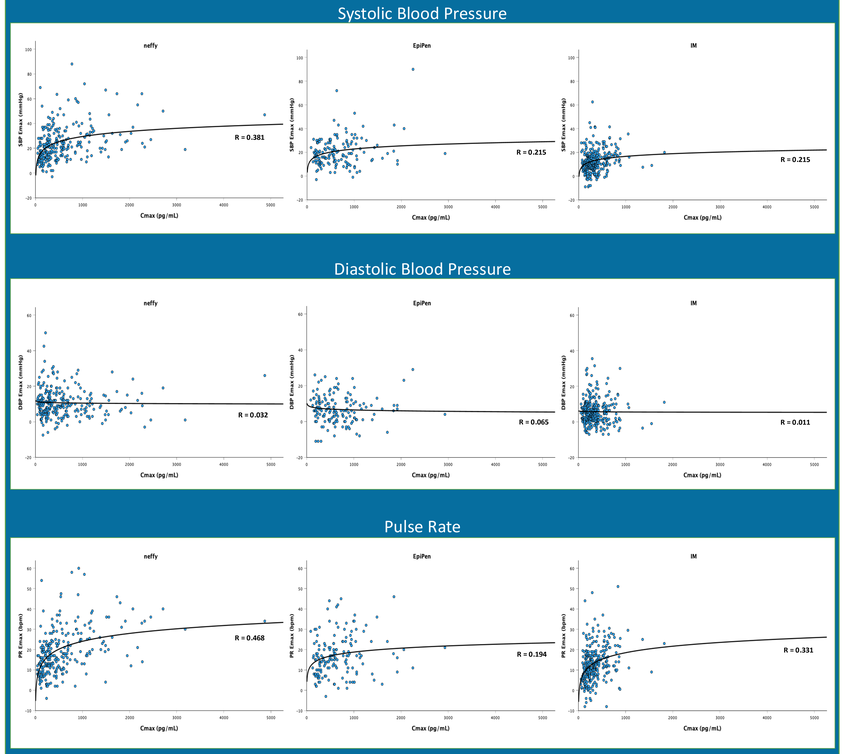
- An integrated analysis was performed using data from four randomized, open-label, single- and/or repeat-dose Phase 1 trials comparing the pharmacokinetic and pharmacodynamic profiles of ***neffy*** (epinephrine nasal spray) 1 and 2 mg, manual epinephrine IM injection 0.3 mg and 0.5 mg, and EpiPen 0.3 mg.
- Three studies enrolled healthy individuals aged 19-55 years; one study enrolled healthy volunteers with a history of type I allergies aged 19-55 years.
- Protocols were approved by the Institutional Review Boards and all the participants gave written informed consent prior to participation.

PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSIS

Blood samples were collected before dosing and up to 360 or 480 minutes after dosing.

Pharmacodynamic measurements (SBP, diastolic blood pressure [DBP], and HR) were assessed before dosing and up to 120 minutes after dosing. Pharmacodynamic data were expressed as change from baseline. The relationship between C_{max} and maximum effect (E_{max})were plotted to evaluate the pharmacodynamic safety in the epinephrine products.

Figure 1: Pharmacokinetic/Pharmacodynamic Relationship: E_{max} vs. C_{max}



Note 1: Lines based on logarithmic model by SPSS.
Note 2: ***neffy*** highest SBP: SBP/DBP 187/87 mmHg @ 30 min (E_{max} 88/25)

RESULTS

BASELINE DEMOGRAPHICS

- Summary demographics of participants is presented in **Table 1**.

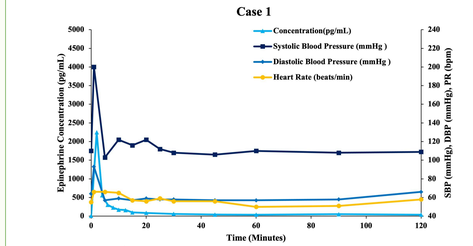
Table 1: Demographic Data

Demographic	Treatment		
	neffy (n=262)	IM (n=312)	EpiPen (n=155)
Age (y)			
Mean (SD)	38.9 (9.5)	38.8 (9.5)	38.2 (9.9)
Median	38	38	37
Minimum, Maximum	19, 55	20, 55	19, 54
Gender, no(%)			
Male	170 (64.9)	185 (59.3)	107 (69.0)
Female	92 (35.1)	127 (40.7)	48 (31.0)

PHARMACOKINETIC/PHARMCODYNAMIC RELATIONSHIP

- Scatter plots of individual relationships between Emax of SBP, DBP, and PR and C_{max} following single and/or repeat doses were generated (**Figure 1**). At concentrations below 1000 pg/mL, SBP and PR increased with epinephrine concentrations.
- Further increases (≥1000 pg/mL) did not translate into additional increases in SBP and HR, except for one case of suspected partial intra-blood vessel injection [SBP increased from 110 to 200 mmHg, with a C_{max} of 2250 pg/mL] (**Figure 2**).

Figure 2: Pharmacokinetic/Pharmacodynamic Relationship: Suspected Intra-Blood Vessel Injection



Note: EpiPen highest SBP: 200/93 mmHg @ 1 min (E_{max} 90/29)

CONCLUSIONS

- When epinephrine is administered parenterally, there appears to be a ceiling effect that limits the cardiovascular response, even at high concentrations.
  - Concentrations of epinephrine >~ 1000 pg/mL do not translate into additional increases in HR or BP.
- We speculate that:
  - Vasoconstrictive effect of epinephrine, largely mediated by α_1 receptor activation, is attenuated by β_2-mediated vasodilation, resulting in a modulation of BP.
  - Increases in HR are limited by compensatory vagal discharge. These ceiling effects are key to the safety of parenteral epinephrine administration.
- These safety mechanisms may be overridden when epinephrine is accidently administered as an intra-blood vessel bolus, resulting in rapid and potentially dangerous increases in BP and HR.

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