Significant Differences in Pharmacokinetic Profiles Among Epinephrine Products – What is the Mechanism for Efficacy?

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RATIONALE

- Randomized clinical trials were not conducted for the approval of epinephrine autoinjectors (EAIs). Instead, their approvals were based on the assumption that epinephrine pharmacokinetics following administration via EAIs was comparable to administration via intramuscular and subcutaneous injection.
- Historically, these epinephrine products have been used interchangeably, with no differentiation in labels and guidance or observed differences in efficacy and safety.
- Extensive clinical experience has demonstrated that all products start working in a few minutes from the epinephrine dosing; however, despite the clinical comparability, recent data have demonstrated notable pharmacokinetic differences among different delivery routes.

METHODS

STUDY DESIGN AND POPULATION

- An integrated analysis was performed using data from five randomized, open-label, Phase 1 trials comparing the pharmacokinetic and pharmacodynamic profiles of the following FDA approved epinephrine injection products: manual epinephrine intramuscular injection 0.3 mg (IM), manual epinephrine subcutaneous injection 0.3 mg (SC), and EpiPen 0.3 mg (EpiPen).
- Three studies enrolled healthy individuals aged 19-55 years and two studies enrolled healthy volunteers with a history of type I 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 480 minutes after dosing. Individual pharmacokinetic 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}).

Pharmacodynamic measurements (systolic blood pressure [SBP], diastolic blood pressure [DBP], and pulse rate [PR]) were assessed before dosing and up to 120 minutes after dosing. Pharmacodynamic data were expressed as change from baseline. For SC, the first timepoint for pharmacodynamic measurements was 15 minutes. There is no data available prior to that.

RESULTS

DEMOGRAPHICS

- The summary demographics of participants is presented in **Table 1**.

Table 1: Demographic Data

Demographic	Treatment		
	IM (n=178)	SC (n=35)	EpiPen (n=77)
Age (y)			
Mean (SD)	38.2 (9.67)	35.5 (9.75)	38.6 (10.2)
Median	38	36	38
Minimum, Maximum	19, 55	19, 55	19, 54
Body Weight			
Mean (SD)	77.4 (11.8)	76.5 (13.6)	80.1 (11.5)
Median	77.8	77.1	80.7
Range	51.3 – 105	51.3 – 105	57.6 – 104
Body Mass Index			
Mean (SD)	26.4 (3.02)	25.5 (3.07)	27.0 (3.34)
Median	26.4	26.0	27.9
Range	19.3 – 32.0	19.8 – 30.0	18.8 – 32.0

PHARMACOKINETICS

- The epinephrine concentration versus time curves are presented in **Figure 1.** EpiPen resulted in the most rapid and pronounced increase in epinephrine levels, while IM and SC had similar profiles.
- Mean C_{max} values followed a similar pattern, with the highest mean concentration observed following EpiPen (581 pg/mL), followed by IM (277 pg/mL) and SC (246 pg/mL). Similarly, EpiPen had the fastest median t_{max} value (10 minutes), while both IM and SC had median t_{max} values of 45 minutes.
- Mean AUC_{last} was generally comparable across treatments. Exposure following EpiPen was 31,600 min*pg/mL, followed by SC (30,200 min*pg/mL), and IM (27,900 min*pg/mL).

PHARMACODYNAMICS

SBP

- EpiPen resulted in the fastest and most pronounced increase in SBP, while only minimal changes were observed following IM. SC resulted in a gradual and less pronounced increase relative to EpiPen.
- The highest mean SBP E_{max} was observed following EpiPen (18.2 mmHg). IM and SC elicited less pronounced increases (11.6 and 11.8 mmHg, respectively).

DBP

- A marked decrease in DBP was observed within 5 minutes of administration of EpiPen and IM. A decrease was also observed following SC; however, the decrease was less pronounced and was not noted until 30 minutes post dose.

PR

- EpiPen also resulted in the fastest and most pronounced increase in PR, while IM resulted in the smallest increase (with the exception of the eight-minute timepoint). SC resulted in a gradual increase that was generally less pronounced relative to EpiPen for the first 60 minutes post-dose.
- As seen with SBP, the highest mean PR E_{max} was observed following EpiPen (14.8 bpm), following by IM (11.5 bpm), and SC (10.9 bpm).

Figure 1: Concentration-Time Profiles of Epinephrine Products

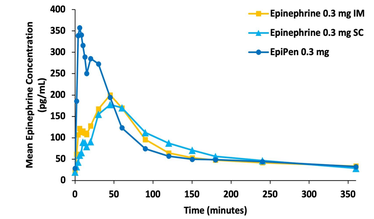


Figure 2: Mean Change from Baseline SBP Versus Time Profiles

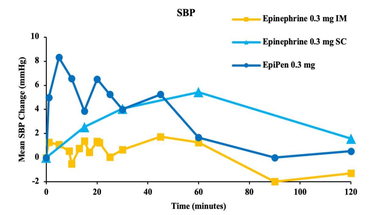


Figure 3: Mean Change from Baseline DBP Versus Time Profiles

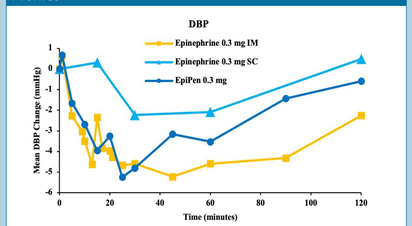
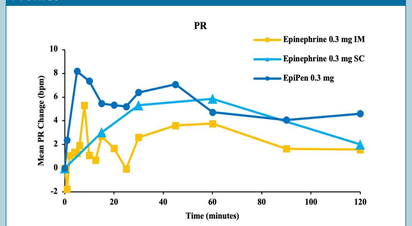


Figure 4: Mean Change from Baseline PR Versus Time Profiles



Note: The first timepoint for PD measurements following SC was 15 minutes.

CONCLUSIONS

- Significant pharmacokinetic and pharmacodynamics differences were observed between EpiPen and IM/SC.
- These differences are not reflected in product labels or treatment guidelines, likely because these PK/PD differences do not translate into any differences in clinical efficacy. As a result, these epinephrine injection products have been used interchangeably.
- Regardless of route of administration, the clinical effects of epinephrine injection are typically observed within minutes of dosing, faster than the T_{max} of any of the approved routes, which suggests epinephrine's therapeutic effects are disaggregated from its pharmacokinetic profile and may occur at concentrations far below the reported C_{max} values.
- Specifically, the activation of the highly sensitive β-adrenergic receptors at lower epinephrine concentrations may drive mast cell stabilization, as well as stimulate chronotropic and inotropic actions. However, α_1-receptor activation vasoconstriction at lower concentrations is poorly understood.

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