Comparison of Pharmacokinetic Parameters and Intra–Blood Vessel Injection Rates Between Manual Intramuscular Injection and Epinephrine Auto-Injectors

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RATIONALE

- Epinephrine auto-injectors (EAIs), such as EpiPen and Symjepi, were approved based on the assumption that their pharmacokinetic (PK) parameters would be similar to manual intramuscular (IM) epinephrine injection; without PK data at the time of approval, there are few studies comparing the PK profiles of EpiPen and Symjepi to manual IM epinephrine injection (epinephrine 0.3 mg)
- Clinically, epinephrine appears to work rapidly following systemic administration, regardless of the route of administration or device
- Recent studies demonstrated that the PK profiles between EpiPen, Symjepi, and manual IM injection are different[1,2]
- Epinephrine delivery via EpiPen resulted in greater early systemic exposure compared with IM injection[3,4]
- Accidental intra–blood vessel injection is a known potential risk of epinephrine injection products and may contribute to unanticipated variations in PK profiles across products

METHODS

- An integrated PK analysis was conducted across 4 randomized crossover clinical trials designed to compare the PK profile of epinephrine 0.3 mg to the anterolateral thigh with EpiPen and Symjepi (ie, EAI comparators)
- Maximum concentration (C_{max}), time to maximum concentration (T_{max}), and the relationship between C_{max} and T_{max} were analyzed to investigate the reasons for the observed PK differences among the injection products
- The rate of suspected intra–blood vessel administration was also assessed for each product
- A total of 175 participants were included in the analysis. All studies were phase 1, open-label, randomized, single-dose, crossover studies. A summary of the individual studies is presented in **Table 1**

Table 1. Summary of Individual Studies Included in the Integrated Pharmacokinetic Analysis

Study	Treatments Included in the Analysis	Subjects
Study 1	*neffy* 1 mg IN Epinephrine 0.3 mg IM	70 healthy volunteers Aged 21-55 years
Study 2	*neffy* 1 mg IN Epinephrine 0.3 mg IM	36 healthy volunteers Aged 19-55 years
Study 3	*neffy* 1 mg IN EpiPen 0.3 mg	36 healthy volunteers Aged 19-54 years
Study 4	*neffy* 1 mg IN EpiPen 0.3 mg Symjepi 0.3 mg	36 patients with type I allergies Aged 21-54 years

IM, intramuscular; IN, intranasal.

RESULTS

C_{max} Values After Injection

- The epinephrine concentration-versus-time curve was higher after EpiPen, followed by Symjepi and epinephrine 0.3 mg IM injection (**Figure 1**)
- The highest geometric mean C_{max} values varied considerably among the 3 products, with the highest concentrations occurring with EpiPen (393 pg/mL), followed by Symjepi (359 pg/mL) and epinephrine 0.3 mg IM (217 pg/mL) (**Table 2**)

T_{max} Values After Injection

- The longest median T_{max} occurred following epinephrine 0.3 mg IM (45 minutes), followed by Symjepi (30 minutes) and EpiPen (20 minutes) (**Table 2**)
- EpiPen was associated with the highest likelihood of a shorter T_{max}, with 21% of subjects exhibiting a T_{max} ≤4 minutes following EpiPen. In contrast, T_{max} values of ≤4 minutes were only observed in 8% of subjects after Symjepi and 7% of subjects following epinephrine 0.3 mg IM (**Table 3; Figure 2**)
- Epinephrine 0.3 mg IM was associated with the highest likelihood of a longer T_{max}, with 28% of subjects exhibiting a T_{max} of >45 minutes following epinephrine 0.3 mg IM. T_{max} values of >45 minutes were observed in 6% of subjects following both Symjepi and EpiPen (**Table 3; Figure 2**)

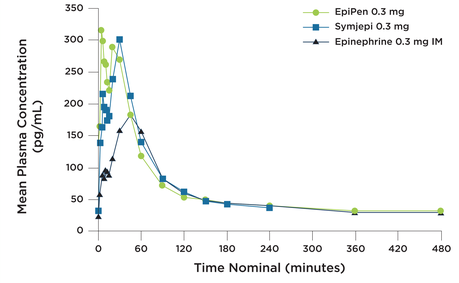
C_{max} Versus T_{max}

- The highest geometric mean C_{max} levels were observed when the T_{max} was ≤4 minutes (**Figure 3**)
  - This relationship between C_{max} and T_{max} was observed for all 3 injection products but was most apparent for EpiPen
- The C_{max} distribution for subjects who had a T_{max} ≤4 minutes suggests that the increase in the highest geometric mean C_{max} in EpiPen for this T_{max} category is likely driven by the proportion of subjects with a C_{max} of >1000 pg/mL (**Figure 4**)

Suspected Intra–Blood Vessel Injections

- The shapes of the concentration-versus-time curve figures for subjects who had C_{max} >1000 pg/mL within 4 minutes of injection (**Figure 5**) demonstrated an immediate sharp peak that appears similar to what would be expected following administration via an intra–blood vessel bolus, suggesting some degree of intra–blood vessel administration
- The ratio of such cases was substantially higher in those who received EpiPen (7/71 injections; 9.9%) compared with both the Symjepi (1/36 injections; 2.8%) and epinephrine 0.3 mg IM groups (0/104 injections; 0%) (**Table 4**)

Figure 1. Mean Plasma Epinephrine Levels Versus Time Following Epinephrine 0.3 mg IM, EpiPen, and Symjepi



IM, intramuscular.

Table 2. Comparison of PK Parameters Across Injection Products (All Cases)

Injection Product	N	C_{max} (pg/mL) Geometric Mean (CV%)	AUC_{0-t} (min*pg/mL) Geometric Mean (CV%)	Median T_{max} (minutes) (range)
Epinephrine 0.3 mg IM	104	217 (61.6)	25,600 (34.8)	45.0 (0.0-360)
Symjepi 0.3 mg	36	359 (77.0)	21,800 (50.2)	30.0 (4.0-90)
EpiPen 0.3 mg	71	393 (82.6)	25,500 (44.6)	20.0 (3.0-154)

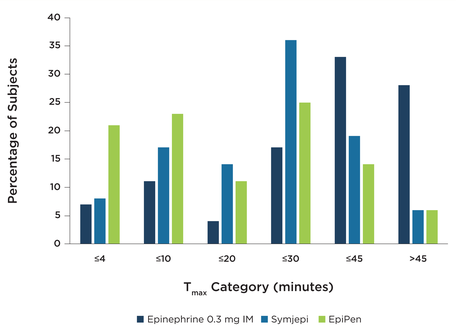
AUC, area under the curve; C_{max}, maximum concentration; CV, coefficient of variation; IM, intramuscular; T_{max}, time to maximum concentration.

Table 3. Percentage of Subjects in Each T_{max} Category

Injection Product	T_{max} Category (minutes) Percentage of Subjects					
	≤4	≤10	≤20	≤30	≤45	>45
Epinephrine 0.3 mg IM	7	11	4	17	33	28
Symjepi 0.3 mg	8	17	14	36	19	6
EpiPen 0.3 mg	21	23	11	25	14	6

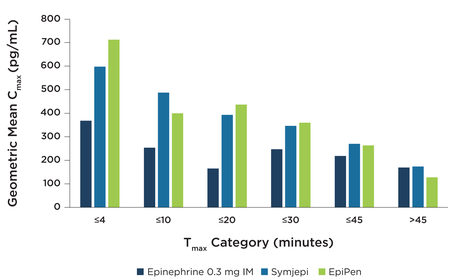
IM, intramuscular; T_{max}, time to maximum concentration.

Figure 2. Distribution of Subjects by T_{max} Category Following Epinephrine 0.3 mg IM, EpiPen, and Symjepi



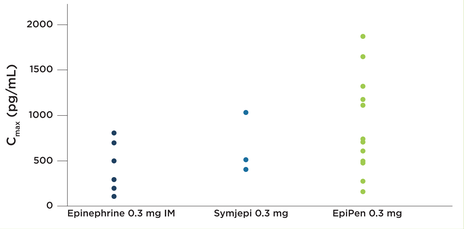
IM, intramuscular; T_{max}, time to maximum concentration.

Figure 3. Mean C_{max} by T_{max} Category Following Epinephrine 0.3 mg IM, EpiPen, and Symjepi



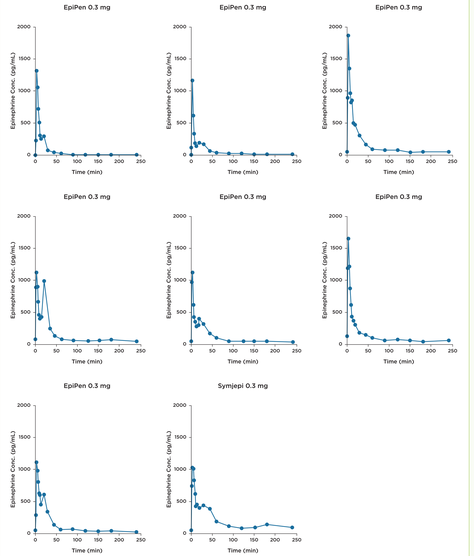
C_{max}, maximum concentration; IM, intramuscular; T_{max}, time to maximum concentration.

Figure 4. Distribution of C_{max} in Subjects With T_{max} ≤4 Minutes



C_{max}, maximum concentration; IM, intramuscular; T_{max}, time to maximum concentration.

Figure 5. Individual Epinephrine Concentration Versus Time for Subjects Reaching Plasma Epinephrine Concentrations of >1000 pg/mL With T_{max} ≤4 Minutes Following EpiPen and Symjepi



IM, intramuscular; T_{max}, time to maximum concentration.

Table 4. Rates of Suspected Accidental Intra–Blood Vessel Administration

Injection Product	Subjects With Suspected Intra–Blood Vessel Administration n/number of injections (%)
Epinephrine 0.3 mg IM	0/104
Symjepi 0.3 mg	1/36 (2.8)
EpiPen 0.3 mg	7/71 (9.9)

IM, intramuscular.

DISCUSSION

- These data represent the most in-depth comparison of the PK profiles of the current epinephrine injection products approved by the US Food and Drug Administration and demonstrate that there are notable differences in the PK profiles of these products
  - These differences have not been previously reported
- The relationship between C_{max} and T_{max} suggests that the highest C_{max} values occur when absorption is the most rapid
- Among injection products, EpiPen demonstrated a faster T_{max}, with a larger C_{max}
  - This may be partially due to the increased likelihood of intra–blood vessel administration observed with EpiPen

CONCLUSIONS

- While manual IM injection, EpiPen, and Symjepi are considered clinically comparable for the treatment of anaphylaxis, we observed differences in the PK profiles that may be partially related to the relative risk of accidental intra–blood vessel administration among the 3 products
- Since bolus administration of epinephrine is associated with significant cardiovascular side effects, clinicians and patients should be aware of the risk of intra–blood vessel injection with EpiPen
- Given that EAIs are most often used in out-of-hospital settings by non-medical professionals, it is important for prescribers to be aware of the differences in injection products and to communicate these differences to their patients

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Presented at the Annual Meeting of the American Academy of Allergy, Asthma and Immunology; February 25-28, 2022; Phoenix, AZ