Intranasal (IN) epinephrine has similar effects on pulse rate as intramuscular (IM) epinephrine

Pharmacokinetic and Pharmacodynamic Relationships of Intranasally Administered and Intramuscularly Injected Epinephrine

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BACKGROUND

While intramuscular (IM) administration of epinephrine (EPI) is a first-line treatment of anaphylaxis, intranasal (IN) EPI may offer a faster route of administration, avoiding reluctance to IM injection and application error.

EPI acts on α- and ß-adrenergic receptors, thus counteracting vasodilation, vascular permeability, and hypotension during anaphylaxis. Because EPI has an intrinsic potential to affect pulse rate (PR) and systolic (SBP) and diastolic blood pressure (SBP) through activation of beta-adrenergic receptors, the pharmacokinetics (PK) and effects of IN administered EPI were compared to IM EPI.

METHODOLOGY

A grouped analysis was performed on data from 3 open-label crossover studies.

During Period 1 of each study, healthy subjects received either of the following treatments:

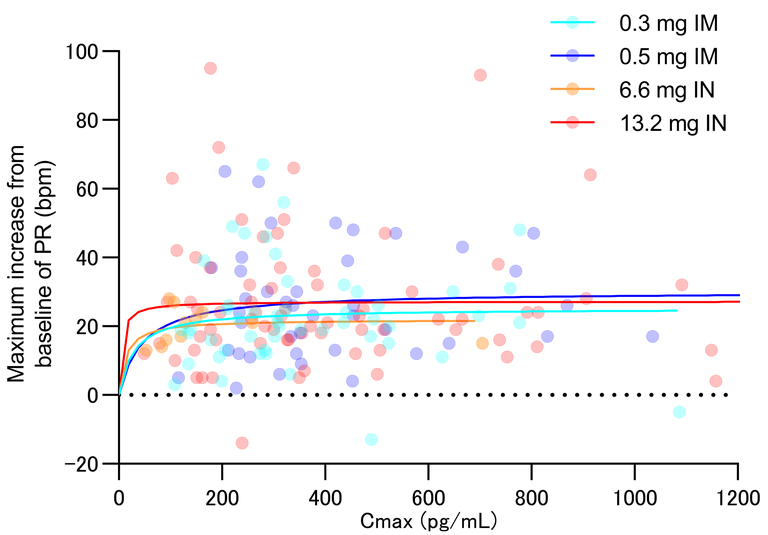
A) IM 0.3 mg EPI by EpiPen® (N=50)
B) IM 0.5 mg EPI by manual syringe (N=42)
C) IN 6.6 mg EPI (as 1 spray) (N=11)
D) IN 13.2 mg EPI (as 2 sprays in opposite nostrils) (N=79)

Maximum EPI concentrations (Cmax) and corresponding maximum changes from baseline (maximum effect, Emax) for PR, SBP and DBP from individual subjects in these studies were combined.

RESULTS

- Relationships between individual EPI Cmax values and maximum increases in PR were similar (Figure 1).
- IN administration of 13.2 mg EPI resulted in higher peak exposure in comparison to IM injected EPI (0.3 and 0.5 mg) and to 6.6 mg EPI administered IN, but total exposure was similar.
- Overall, there were no statistical or clinically meaningful differences in PR, SBP or DBP across all treatment groups (IN- and IM-administered EPI).
- All treatments were well tolerated and no serious or unexpected Adverse Effects were reported.

Relationship between EPI Cmax and maximum increase of PR



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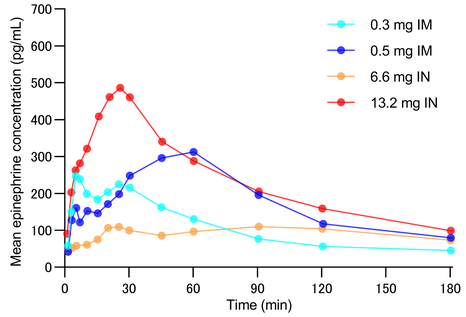

Table 1. EPI PK parameters

	EpiPen (0.3mg)	IM manual syringe (0.5mg)	IN (6.6mg)	IN (13.2mg)
N	50	42	11	79
Cmax (pg/mL): Mean (CV%)	368 (54.9)	847 (329.5)	178 (98.2)	634 (142.5)
AUC_{0-t} (min*pg/mL): Mean (CV%)	25629 (26.8)	44095 (31.5)	25936 (129.8)	56419 (98.1)
Tmax Median (min): (range)	20 (2-60)	60 (3-180)	21 (2-120)	23 (1-180)

Table 2. EPI maximum effects, mean (SD)

	EpiPen (0.3mg)	IM manual syringe (0.5mg)	IN (6.6mg)	IN (13.2mg)
N	50	42	11	79
PR (bpm)	22.9 (14.7)	26.7 (15.6)	19.8 (4.95)	26.8 (18.8)
SBP (mmHg)	17.8 (10.7)	15.8 (9.26)	14.0 (11.3)	16.3 (12.6)
DBP (mmHg)	11.5 (6.96)	10.6 (6.92)	11.5 (8.48)	10.7 (7.92)

CONCLUSION

- IN administered EPI (6.6 and 13.2 mg) has comparable effects on PR, SBP, and DBP as IM-injected EPI (0.3 and 0.5 mg), with similar variability and maximum effects.
- The apparent plateau of EPI effects on cardiovascular parameters at the attained plasma concentrations aligns with findings published by others.

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