Safety and Pharmacokinetics of 0.3mg / 0.5mg Epinephrine Injection by Autoinjector in Food-allergic Teenagers: A Randomized Cross-over Trial

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INTRODUCTION

- There are limited data on the pharmacokinetics of intramuscular epinephrine used to treat anaphylaxis.
- Epinephrine autoinjectors (EAIs) licensed for adults in the USA deliver 0.3mg epinephrine, yet international guidelines recommend a dose of 0.5mg to treat anaphylaxis in teenagers and adults.

METHODS

- We undertook a single-blind, randomised cross-over study assessing the pharmacokinetics and pharmacodynamics of 0.3mg and 0.5mg injection of Epinephrine using an EAI (Emerade®) in food-allergic teenagers at risk of anaphylaxis.
- Participants self-administered each device over 2 hospital visits, at least 1 month apart (order randomised by computer allocation).
- Injection was confirmed by ultrasound (Figure 1).
- Blood samples were drawn from an in-dwelling intravenous cannula, sited 1 hour prior to injection.
- Participants underwent cardiovascular monitoring throughout.
- *Clinicaltrials.gov NCT03366298; Eudra CT: 2017-003239-13*

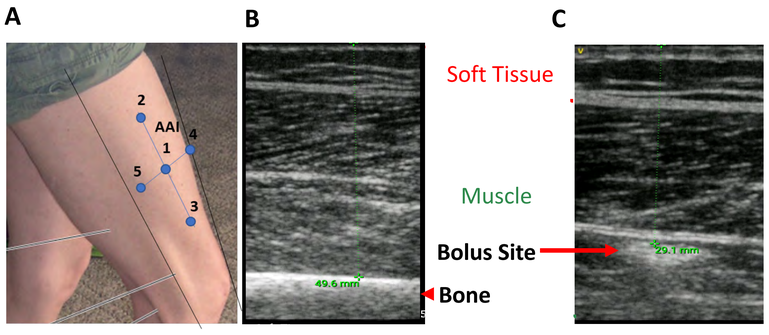
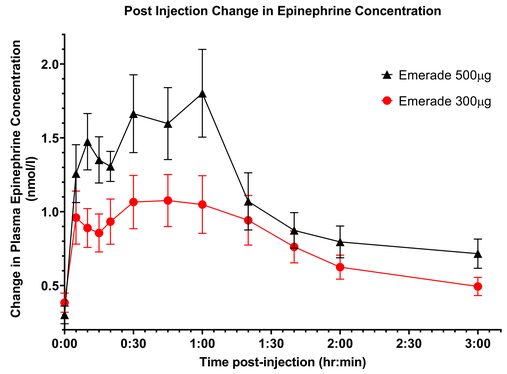


Figure 1 (A) Sites for USS assessments; USS image before (B) and after (C) injection using autoinjector.

RESULTS

- Twelve participants (58% male, median age 15.4 years) participated.
- Median weight: 61.8kg (range: 41.8-76.4kg).
- Intramuscular injection resulted in a biphasic plasma epinephrine profile.
- The 0.5mg dose resulted in a higher peak (p=0.01) and more favourable plasma epinephrine profile (AUC p<0.05) compared to 0.3mg.
- Peak plasma epinephrine levels were maintained for up to an hour after administration.



	Max conc^{n} (C_{max}) nM	Time to peak (T_{max})	AUC (nM.hr)
300µg	1.56	45mins	9.8
500µg	1.98	53mins	12.2
	p=0.03	p=0.72	p=0.02

Figure 2. Epinephrine absorption. Data are mean (95% CI)

- A trend towards greater and more sustained increases in cardiac output and stroke volume were noted with the 0.5mg dose (Figure 3)
- Doses were well tolerated with no significant adverse events and no significant differences noted between either dose (Table 1)

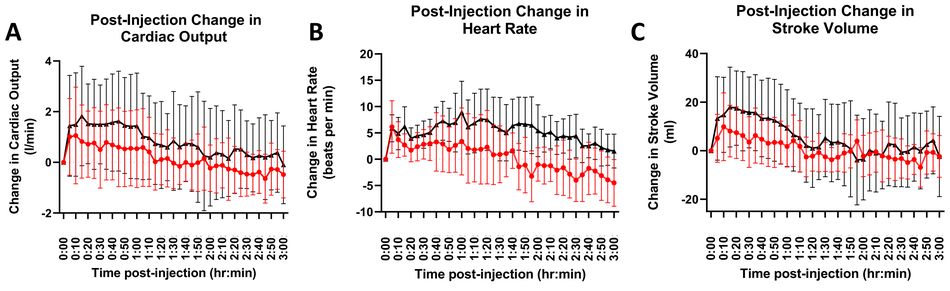


Figure 3. Time-course of cardiovascular parameters post-injection. a) cardiac output, b) heart rate, c) stroke volume

Adverse Events	Total n=24		Emerade 300 (n=12)	Emerade 500 (n=12)
Local symptoms/signs	%	n	n	n
Pain (injection site/thigh)	58	14	8	6
Bleeding				
Minimal	12.5	3	2	1
Minor	8.3	2	1	1
Discolouration of skin at injection site	4.2	1	0	1
Symptoms/signs distant from injection site				
Any non-local symptoms	54.2	13	4	9
Subjective jitteriness/Objective tremor	41.7	10	3	7
Sensation of heart beat faster/stronger	29.1	7	3	4
Headache/subjective neuro	12.5	3	2	1
24hour follow up				
Bruise	4.2	1	1	0
Leg ache	8.3	2	2	0

Table 1. Summary of adverse events.

CONCLUSIONS

- Compared to 0.3mg, injection with 0.5mg epinephrine resulted in:
  - a more favourable plasma epinephrine profile
  - beneficial cardiovascular consequences

  without increasing adverse events.
- Given these data, there is a clear rationale for the provision of EAI at a 0.5mg dose to treat anaphylaxis in the community.

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