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INVITED REVIEW

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Pharmacokinetics of adrenaline autoinjectors

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Abstract

Anaphylaxis is a medical emergency with adrenaline acknowledged as the first-line therapy. It is therefore important that patients have access to self-injectable adrenaline in the community. Manufacturers have been requested by European Medicine Regulators to generate pharmacokinetic data for these autoinjector devices. For the first time, these data provide an insight into how individual devices work in different populations, and how they compare. We undertook a thorough literature search and also accessed grey literature, using searches of medicine regulators' websites and freedom of information requests. The data demonstrate that it takes at least 5–10 min to achieve early peak plasma concentration for most devices. The specific autoinjector device seems to be the most important determinant of pharmacokinetics, with different devices giving rise to different plasma adrenaline profiles. Needle length does not seem to be the most important factor; rather, the force and speed of injection (which varies from one device to another) is likely to be of greater importance. In general, peak plasma adrenaline concentration is lower and time-to-peak concentration longer with increased skin-to-muscle depth. However, it is difficult to draw conclusions with the current available data, due to a lack of head-to-head comparisons, small numbers of study participants and the failure to acknowledge the biphasic nature of intramuscular adrenaline absorption for analysis purposes.

KEYWORDS
anaphylaxis, autoinjectors, pharmacokinetics

1 | INTRODUCTION

Anaphylaxis is an important medical emergency, with an estimated prevalence worldwide of 1–761 per 100 000 person-years for all causes.[1] Hospital admissions due to anaphylaxis are increasing globally; the most common triggers are foods such as peanut tree nuts and milk, wasp and bee stings and medications.[2,3] Presentations usually involve respiratory distress and/or cardiovascular collapse, but rarely result in fatal outcomes.[3–6] The mainstay of longer-term management is avoidance of the trigger.[7,8] This can be challenging, particularly for food allergy, with the issues around allergen labelling[9] which impact adversely on quality of life.[10] The evidence base for the acute management of anaphylaxis is weak, but there is a global consensus that intramuscular (IM) adrenaline is the treatment of choice.[7,8,11,12]

In community settings, adrenaline can be provided for emergency use as an adrenaline autoinjector (AAI) device,[7,8] although these are not available in many countries.[13] Carrying an AAI enables IM adrenaline to be rapidly administered by the patient or a lay person. There have, however, been concerns that with some AAIs having shorter needle lengths, this could result in a subcutaneous rather than IM dose in many individuals.[14] In 2015, the Committee for Medicinal Products for Human Use (part of the European Medicines Agency) undertook a review in this area,[15] noting that a number of different factors could influence the delivery of adrenaline via an AAI: 'needle

length, the thickness of fat under the skin, the way the autoinjector works (e.g., if it is spring loaded or not), the angle at which the device is placed on the skin and the force used to activate the device as well as how well the user follows the instructions for injection'. The European Medicines Agency asked manufacturers to generate data to allow a better understanding of the pharmacokinetics (PK) of adrenaline delivery by autoinjectors (Box 1). These data were expected to substantially add to the previously published data.

In this review, we present a summary of the PK data now available for AAIs. We searched both published literature and grey literature to collate the evidence (Box 2) and reviewed, discussed and synthesized the available data to inform our clinical approach to managing patients at risk of anaphylaxis.

Key Messages

- The early peak plasma concentration occurs at 5–10 min for most adrenaline autoinjector devices.
- Injection force and speed may be more important than needle length for determining adrenaline pharmacokinetics.
- Peak plasma adrenaline concentrations are generally lower and time-to-peak concentration longer with increased skin-to-muscle depth.

2 | PHARMACOKINETIC (PK) STUDIES OF ADRENALINE AUTOINJECTORS

A total of nine studies were identified in the literature (Table 1): six were published in peer-reviewed journals,[17–22] one is currently published as an abstract[23] while the last two were available from national regulatory bodies.[24–30] The four older studies were from the same group, the first 3 focusing on first-generation Epipen (future references to Epipen are second generation device unless otherwise stated),[17–19] and the fourth comparing second generation Epipen to Auvi-Q.[20] Included participants were either children at risk of anaphylaxis[17,19] or healthy adults.[18,20] Amongst more recent studies, all bar one[23] were undertaken by manufacturers in response to the 2015 EMA request.[21,22,27–30] Only one study included a comparison of devices produced by different manufacturers,[27] while one compared different doses with the same device[23]; otherwise, the comparison was to adrenaline given by needle and syringe.

Notably, a consistent feature across all studies is the considerable 'noise' in the PK parameters as evidenced by the coefficients of variation in the reported data. In addition, the three oldest studies (all by the same group) report 10-fold greater plasma adrenaline concentrations[17–19] than more recent studies, including a study by the same group in 2013[20]; the reasons for this are not clear. Of note, there is a high level of consistency in peak plasma adrenaline concentrations across more recent studies, which implies a possible difference in the assay used in the earlier studies.

BOX 1 Glossary box

Bioequivalence: The US Food and Drug Administration define this as the absence of a significant difference in the rate and extent to which the active ingredient becomes available at the site of drug action when administered at the same molar dose under similar conditions.[16]

Pharmacokinetics (PK): The absorption, distribution, metabolism and excretion of a drug (i.e. the effect of the body on a drug). See Figure 1 for further information.

Pharmacodynamics (PD): The effect of a drug and the mechanism of its action in the body.

BOX 2 Literature search strategy

OVID Medline searched 24th December 2020: (adrenaline.mp OR Epinephrine/) AND (autoinjector.mp OR anapen.mp OR emerade.mp OR epipen.mp OR jext.mp) AND (pharmacokinetics.mp OR delivery).

Grey literature: searched world wide web for summary of product characteristics for adrenaline autoinjectors; search of European medicine regulator websites; freedom of information request for pharmacokinetic data submitted to the Medicines and Healthcare products Regulatory Agency in the United Kingdom, in response to the European Medicine Agency's 2015 data request.[15]

3 | IMPACT OF SKIN-TO-MUSCLE DEPTH

Four studies—all commercially funded—attempted to evaluate the impact of body mass index, using the parameter of skin-to-muscle depth (STMD), assessed by ultrasound (Table 2).[21–23,27] These studies categorized participants (healthy adults) into subgroups with low (<15 mm), moderate (15–20 mm) and high (>20 mm) STMD. With the exception of the study commissioned by the manufacturer of Anapen,[21] all had a crossover design. Unfortunately, the numbers in each subgroup were too few to be powered to detect any small differences between groups.

Two studies evaluated Epipen[22,27]: one (manufacturer-funded)[22] demonstrated no discernible impact of STMD on PK parameters (Cmax, Tmax) (Figure 1) although there was a trend towards increasing Tmax (i.e., time-to-peak adrenaline) with increasing STMD (Table 2).[22] A second study by the manufacturer of a different device found similar findings (Figure 2, Tables 2 and 3).[27]

For Emerade, there was a trend towards a quicker and higher Cmax in patients with STMD ≤15 mm, but no obvious impact due to higher STMD despite Emerade having a longer needle length (23 mm) compared with other devices (Table 2).[27] The PK profile in the low STMD cohort was consistent with that seen in an independently funded study using Emerade in teenagers (Table 1).[23]

The manufacturer's study assessing Anapen compared PK profile in 18 normal weight men with 12 overweight women (all with STMD >15 mm), in a non-crossover design (Table 2).[21] A clear difference was seen between the 2 groups, with a faster and greater increase in plasma adrenaline in the normal weight men.

With respect to Jext, limited information from the manufacturer's study was obtained from the UK Regulator through a freedom of information request (Table 2).[30] There was significant evidence of a delay in adrenaline absorption with increasing STMD, prompting a rewording of the manufacturer's summary of product characteristics (SmPC) to state: 'adrenaline absorption in patients with a thick subcutaneous fat layer (i.e., STMD, skin-to-muscle depth >20 mm) is slower than in subjects with a thinner subcutaneous fat layer'.[28,29] Furthermore, this was also observed for when comparing PK parameters for Jext and IM injection using a needle/syringe. While data were comparable for the first 16 min across all cohorts, when evaluated for PK profile up to 30 min after injection, plasma adrenaline was significantly lower for Jext compared with manual IM injection in the STMD >20 mm cohort (Tables 2 and 3). This observation is also reflected in changes to the wording in the Jext SmPC and is consistent with data comparing Emerade, Epipen and Jext (in the study funded by the manufacturer of Emerade).[27]

Interestingly, $AUC_{0\text{-last}}$ for plasma adrenaline (which reflects overall absorption/elimination for at least 3 h after injection) is generally greater with increasing STMD: this was seen for Emerade 500 mcg (but not 300 mcg),[27] Epipen 0.3 mg[22,27] and possibly for Jext 300 mcg[27,30](Figure 3, Table 2). Participants with a higher STMD seem to have a larger, delayed second peak in Cmax, around 1 h after injection. One possible explanation is that adrenaline may induce transient local vasoconstriction at the site of injection, which causes a 'modified release' phenomenon (in much the same way that co-injection with adrenaline is often used to prolong the effect of local anaesthesia).[31] This may be amplified in individuals with higher STMD, as the growth factors associated with increased adiposity also result in vascularization.[32]

Skin-to-muscle depth varies with sex, with higher STMD reported in females compared with males of equivalent body mass index.[33] Controlling for STMD, females tended to have a greater Cmax and $AUC_{0\text{-last}}$ compared to males following injection with Epipen, although the number of participants in each subgroup was too small to reach statistical significance.[22] A similar comparison in the unpublished study by the manufacturer of Emerade is less clear, although perhaps demonstrates a trend towards females having higher Cmax than males with a similar STMD.[27]

In summary, the available data suggest that absorption of adrenaline following percutaneous injection into the mid-thigh in patients with higher STMD is often delayed, with a lower initial peak concentration and a longer time-to-maximum concentration. This potentially means that individuals with higher STMD have a significantly lower plasma adrenaline in the first 20–30 min after injection with an AAI. Unfortunately, analysis of PK data in each report is hampered by the lack of recognition of a biphasic profile to the absorption of adrenaline given by IM injection, something well-established in the literature. The data are also confounded by significant intra- and inter-individual variability in PK outcomes, relatively small cohort sizes and a consequential absence of formal statistical testing.

4 | NEEDLE LENGTH AND INTRAMUSCULAR VERSES SUBCUTANEOUS INJECTION

The impact of increasing STMD on the delivery of adrenaline may in part be explained by whether adrenaline is delivered intramuscularly or subcutaneously. Studies have attempted to investigate this by comparing AAI with different needle lengths, or syringes attached to needles of different lengths. The 2001 study by Simons et al compared first-generation Epipen 0.3 mg with a similar dose given subcutaneously.[18] Unfortunately, the results are confounded as the Epipen was given in the thigh while the subcutaneous dose was given over the deltoid muscle in the arm.

The manufacturer of Emerade compared the PK profile following 0.5 mg adrenaline injected using needle/syringe by the IM versus subcutaneous route in the anterolateral thigh (using ultrasound guidance) in a crossover design.[27] IM injection resulted in an approximately threefold higher plasma adrenaline concentration at 3 min and 1.7-fold higher concentration at 5 min post-injection, indicating slower absorption by the subcutaneous route.[27] However, these data are potentially confounded by the much narrower gauge needle used for subcutaneous (27G, internal diameter 0.21 mm) versus IM injection (18G, 0.84 mm): this equates to a higher flow rate in the 27G needle of >250 times (Hagen-Poiseuille equation). The impact of a lower velocity of injection seen with the needles used for subcutaneous injection cannot be easily unpicked from the impact of IM versus subcutaneous delivery of adrenaline.

This manufacturer study also compared Epipen and Jext (which have 15mm/16mm needles, respectively) to Emerade (23 mm needle); a reasonable assumption would be that the former would not deliver an IM injection in subjects where the STMD exceeds the needle length.[27] However, Emerade did not result in a more favourable plasma adrenaline profile. In fact, absorption was significantly better and faster (i.e., not bioequivalent) with Epipen, and paradoxically, this was most evident in patients with higher STMD (Table 3).[27] Curiously, this was not seen for Jext, despite the fact that Epipen and Jext are often considered to be similar devices: the PK profile for Jext was statistically bioequivalent to Emerade (Table 3). The manufacturer of Anapen reported that adrenaline absorption was better (with higher Cmax) following injection with Anapen (11-mm needle)

TABLE 1 Summary of adrenaline autoinjector pharmacokinetic studies

			Pharmacokinetics for all participants				
			Data estimated from graphs in report				Data reported in text
			First peak		Second peak		
Study	Participants details and study design	Device	$Cmax_1$ (ng/ml)	$Tmax_1$ (min)	$Cmax_2$ (ng/ml)	$Tmax_2$ (min)	Cmax (ng/ml)
Simons 1998 Canada[17]	17 children, 4-12 y with food allergy Parallel design	Epipen (1st gen) 0.3 mg Syringe SC 0.01 mg/kg (max 0.3 mg)	1.56 ± 0.28 0.84 ± 0.20	5 5	1.08 ± 0.41 0.86 ± 0.26	20 40	2.14 ± 0.35 1.80 ± 0.21
Simons 2001 Canada[18]	13 healthy adults (18–35 y, male) Crossover design	Epipen (1st gen) 0.3 mg MT Syringe 0.3 mg IM MT Syringe 0.3 mg IM A Syringe 0.3 mg SC A	7.5 ± 3.1 7.3 ± 5.0 1.2 ± 0.4 1.2 ± 0.4	10 10 60 120	6.2 ± 3.0 4.4 ± 1.0 1.8 ± 0.4 1.6 ± 0.4	45 90 180 120	12.2 ± 3.8 9.7 ± 4.8 1.8 ± 0.4 2.9 ± 0.6
Simons 2002 Canada[19]	10 children, 5–8 y with food allergy Parallel design	Epipen (1st gen) 0.15 mg Epipen 0.3 mg	1.9 2.3 ± 0.6	20 30	1.8 ± 1.1 2.2 ± 1.0	45 75	2.0 ± 0.5 2.3 ± 0.4
Manufacturer's study (Auvi-Q)* [Edwards] 2013 Canada[20]	71 healthy adults (18–45 y, male) Higher-order crossover design	Auvi-Q 0.3 mg Epipen (2nd gen)	0.40 ± 0.26 0.45 ± 0.32	5 5	0.32 ± 0.16 0.28 ± 0.14	30 30	0.49 0.52
Manufacturer's study (Emerade) 2018 Germany[27]	8 healthy adults Crossover design	Syringe 0.3 mg IM Syringe 0.3 mg SC	0.23 ± 0.27 0.22 ± 0.14	5 10	0.45 ± 0.10 0.50 ± 0.14	60 60	NR NR
	40 healthy adults Crossover design	Emerade 0.3 mg Emerade 0.5 mg Epipen (2nd gen) 0.3 mg Jext 0.3mg	~0.12 ~0.16 ~0.25 ~0.16	5–10 5–8 5–12 5–15	~0.22 ~0.37 ~0.26 ~0.22	60 50–60 30–40 30–40	0.252 0.372 0.386 0.266
Manufacturer's study (Anapen) Duvauchelle 2018 France[21]	18 healthy men with BMI 18–26 Crossover design	Anapen 0.3 mg, MT Syringe 0.3 mg MT Syringe 0.5 mg, MT Anapen 0.3 mg LT	0.26 ± 0.07 0.16 ± 0.06 0.35 ± 0.07 0.29 ± 0.07	6 4 6 6	0.29 ± 0.04 0.32 ± 0.05 0.43 ± 0.04 0.33 ± 0.04	40 50 50 40	0.45 ± 0.06 0.40 ± 0.05 0.58 ± 0.06 0.47 ± 0.06
	12 women with BMI >26	Anapen 0.3 mg, LT	0.14 ± 0.13	2	0.29 ± 0.05	50	0.53 ± 0.11
Patel 2020 UK[23]	12 teenagers at risk of anaphylaxis Crossover design	Emerade 0.3 mg Emerade 0.5 mg	0.181 (0.12,0.28) 0.320 (0.26,0.39)	9.6 (5.3,17.4) 8.5 (6.1,11.8)	0.208 (0.26,0.39) 0.359 (0.27,0.48)	50 (35,72) 50 (40,63)	0.218 (0.13,0.36) 0.394 (0.31,0.50)
Manufacturer's study (Epipen) Worm 2020 Germany '22]	35 healthy adults Crossover design	Epipen (2nd gen) MT Epipen (2nd gen) LT Syringe MT	0.33 ± 0.04 0.26 ± 0.05 0.13 ± 0.02	6 8 8	0.32 ± 0.03 0.31 ± 0.04 0.28 ± 0.03	30 30 40	0.52 ± 0.04 0.41 ± 0.03 0.35 ± 0.05
Manufacturer's study (Jext) (SmPC; FOI request to MHRA)[30]	23 healthy adults Higher-order crossover design	Jext 0.3 mg Syringe 0.3 mg	NR NR	8–10 NR	NR NR	30–40 NR	0.242 0.244

Note: Data are mean (± standard error) unless otherwise stated. Units unified where possible. Many reports do not specify whether means are geometric or arithmetic, which may explain apparent discrepancies between graphs and data reported in tables. ♦Median. [§]Tmax reported is for first 20 mins. *Authors state that Auvi-Q and EpiPen were bioequivalent; see Table 3 for bioequivalence data for other devices.

Abbreviations: A, arm; IM, intramuscular; LT, lower thigh; MT, mid-thigh; SC, subcutaneous; SmPC, summary of product characteristics; STMD, skin-to-muscle depth.

Tmax (min)	Reported $AUC_{0\text{-last}}$ (h.ng/ml)	Comments	Investigated: *Dose*	*Location*	*IM vs SC*	*STMD*	*Needle length*	*Safety/AEs*
8 ± 2 34 ± 14	1.80 ± 0.30 1.12 ± 0.22	Sampled for 180 min Injection site not specified			✓			✓
NR NR NR NR	NR NR NR NR	Sampled for 180 min Injection sites: MT = mid-thigh A = arm		✓	✓			
16 ± 3 15 ± 3		Sampled for 180 min More adverse events with 0.3 mg	✓					✓
5 5	0.536 0.466	Sampled for 360 min Bioequivalence demonstrated						✓
NR NR	AUC was greater for SC>IM	Sampled for 180 min. Flow rate via needle for SC is x256 > than that for IM injection			✓	✓		
60♦ 50♦ 25♦ 40♦	0.342 0.532 0.411 0.370	Sampled for 180 min	✓			✓	✓	
12.6 ± 1.7§ 10.8 ± 1.8§ 9.0 ± 1.6§ 9.0 ± 1.1§	0.459 ± 0.030 0.503 ± 0.047 0.777 ± 0.074 0.473 ± 0.033	Sampled for 240 min Injection sites: MT = mid-thigh LT = lower thigh	✓	✓			✓	
14.4 ± 1.7§	0.678 ± 0.046	Sampled for 240 min				✓	✓	
$Tmax_1$: 9.6 $Tmax_2$: 50 $Tmax_1$: 8.5 $Tmax_2$: 50	0.174 (0.86,0.35) 0.387 (0.26,0.57)	Sampled for 180 min Data are geometric means with 95% CI Data for Epipen not reported in abstract	✓				✓	✓
23 ± 4 27 ± 4 43 ± 3	0.50 ± 0.04 0.47 ± 0.04 0.44 ± 0.03	Sampled for 360 min Longer needles used for participants with high STMD to ensure IM delivery		✓		✓		✓
8–10 NR	0.311 0.234	Sampled for 180 min Longer needles used on participants with higher STMD.				✓		

TABLE 2 Impact of skin-to-muscle depth on pharmacokinetics of adrenaline autoinjectors

			Pharmacokinetics for all participants							
			Data estimated from graphs in report				Data reported in text			
			First peak		Second peak					
Study	Participants details and study design	Device	$Cmax_1$ (ng/ml)	$Tmax_1$ (min)	$Cmax_2$ (ng/ml)	$Tmax_2$ (min)	Cmax (ng/ml)	Tmax (min)	Reported $AUC_{0\text{-last}}$ (h.ng/ml)	Main findings
Manufacturer's study (Emerade) 2018 Germany[27]	40 healthy adults Crossover design	Emerade 0.3 mg Low STMD Mod. STMD High STMD Emerade 0.5 mg Low STMD Mod. STMD High STMD EpiPen 0.3 mg Low STMD Mod. STMD High STMD Jext 0.3 mg Low STMD Mod. STMD High STMD	0.165 0.100 0.075 0.155 0.135 0.180 0.265 0.255 0.225 0.225 0.090 0.170	2 12 12 5 5 15 5 12 15 5 5 15	0.270 0.180 0.190 0.400 0.290 0.460 0.240 0.265 0.310 0.255 0.205 0.200	50 60 60 50 50 60 40 20 40 40 50 75	0.299 0.220 0.228 0.356 0.342 0.543 0.415 0.369 0.363 0.308 0.227 0.276	50 60 45 50 50 60 20 20 40 40 50 50	0.354 0.330 0.342 0.498 0.487 0.851 0.367 0.417 0.506 0.370 0.357 0.398	High level of inter-individual variability which limits the conclusions which can drawn. For all 3 devices, there was evidence of a delay in initial absorption kinetics with increasing STMD (indicated by a delay in $Tmax_1$); this was apparent evident for Emerade and Jext, where there was a trend towards a lower $Cmax_1$ with STMD >20 mm.
Manufacturer's study (Anapen) Duvauchelle 2018 France[21]	18 men, BMI 18–26, 12 women, BMI >26 Parallel design	Men, STMD<15 mm Women, STMD>15 mm	0.29 ± 0.07 0.14 ± 0.13	6 2	0.33 ± 0.04 0.29 ± 0.05	40 50	0.47 ± 0.06 0.53 ± 0.11	9.0 ± 1.1[§] 14.4 ± 1.7[§]	0.473 ± 0.033 0.678 ± 0.046	Comparison is for injection at lower thigh. No obvious difference in PK profile.
Manufacturer's study (Epipen) Worm 2020 Germany[22]	35 healthy adults Crossover design	Epipen (2nd gen) MT Low STMD Mod. STMD High STMD	0.38 ± 0.07 0.38 ± 0.08 0.39 ± 0.08	7 5 15	0.31 ± 0.04 0.33 ± 0.05 0.34 ± 0.07	30 30 25	0.52 ± 0.08 0.50 ± 0.07 0.53 ± 0.08	9.0♦ 10.5♦ 30.0♦	0.47 ± 0.04 0.44 ± 0.06 0.60 ± 0.07	Trend towards delayed absorption with increasing STMD, but no reduction in Cmax itself.
Manufacturer's study (Jext) (FOI request to MHRA)[30]	23 healthy adults Higher-order crossover design	Jext 0.3 mg Low STMD Mod. STMD High STMD	NR NR NR	NR NR NR	NR NR NR	NR NR NR	0.300 0.211 0.215	30♦ 12♦ 60♦	0.312 0.243 0.378	$AUC_{0\text{-}30}$ was significantly lower with increasing STMD, implying a delay in absorption kinetics with increasing STMD: 27% and 64% lower in Mod and High STMD cohorts, respectively

Note: Figures are means (standard error) unless stated otherwise. Units unified where possible. ♦Median. Low STMD: <15 mm; moderate STMD: 15–20 mm; high STMD: >20 mm.

Abbreviations: NR, not reported; STMD, skin-to-muscle depth.

compared with an equivalent dose given via a syringe and a longer needle (25 mm) (Figure 3).[21] Thus, needle length alone does not appear to impact on higher plasma adrenaline concentrations achieved after administration.

5 | IMPACT OF DEVICE

One possible explanation for these data is the possibility that the device mechanism is a factor in terms of PK profile. Some AAI have a spring-based system (which may be under high or low tension) while others are cartridge-based (which in turn may be spring-based or gas-powered). The manufacturers of Emerade undertook a comparison of Emerade, Epipen and Jext (all at 0.3 mg).[27] Emerade is a (high tension) syringe-based device. Epipen, a cartridge-base device, resulted in a significantly higher Cmax and quicker time-to-peak concentration compared to Emerade.[27] While Jext (cartridge-based) also resulted in a higher mean Cmax compared with Emerade, this was not statistically significant and Jext and Emerade were found to be bioequivalent. Injection with all three devices resulted in a clear biphasic absorption

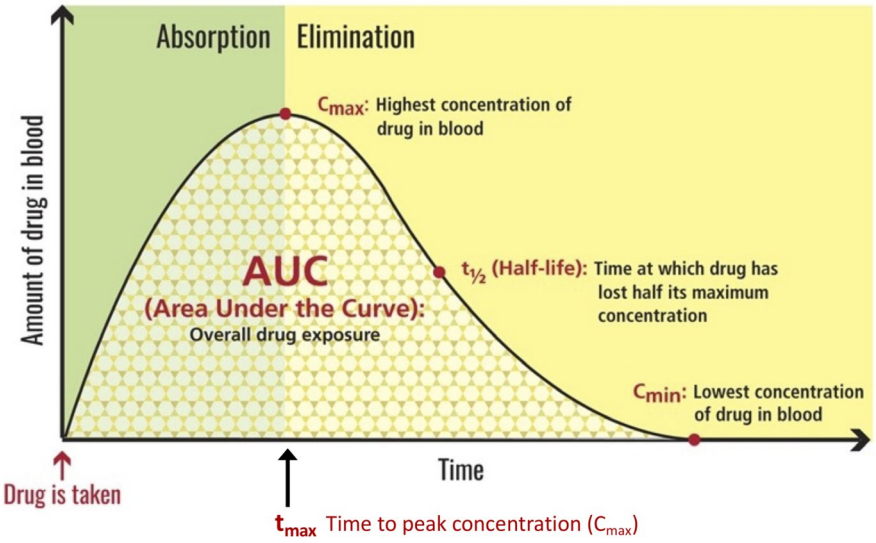

FIGURE 1 Typical PK absorption profile for a drug. AUC, area under curve; Cmax, maximum plasma concentration achieved; Tmax, time to Cmax. The AUC gives best approximation of overall pharmacokinetic profile

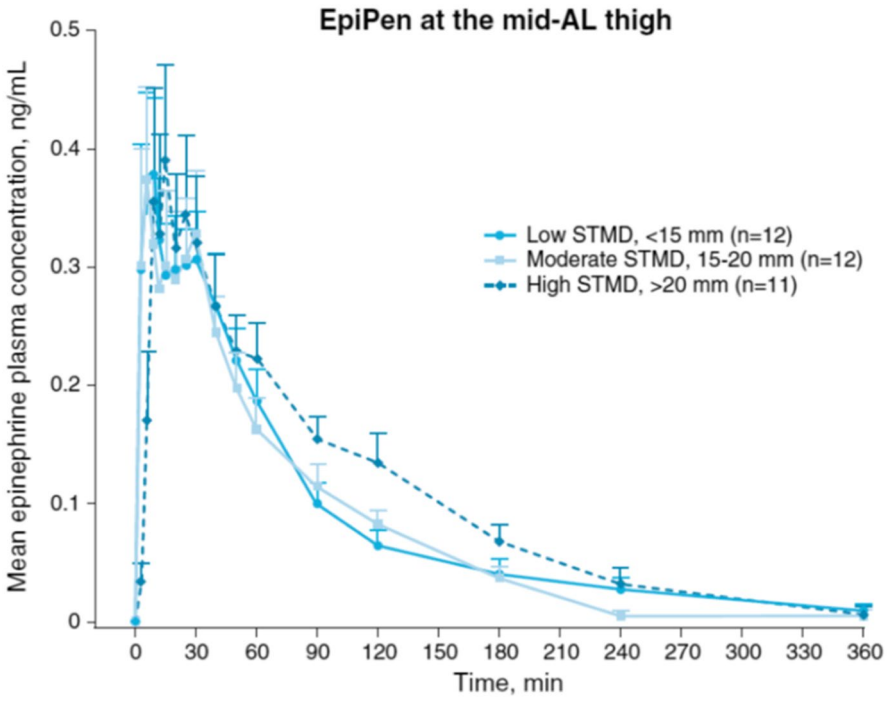

FIGURE 2 A Pharmacokinetics of EpiPen missing. Reproduced from Worm et al 2020[22] under Creative Commons CC BY license. Detail of first and second peak obscured by the wide coverage of the time axis

TABLE 3 Reported bioequivalence data for PK parameters according to skin-to-muscle depth

	Cohorts		
	STMD <15 mm	STMD ≥15 mm–≤20mm	STMD >20 mm
Emerade 0.3 mg compared to Jext 0.3 mg[27]			
Cmax	Across all 3 cohorts: 0.94 (0.81–1.08)		
$AUC_{0\text{-last}}$	Across all 3 cohorts: 0.92 (0.84–1.01)		
Emerade 0.3 mg compared Epipen 0.3 mg[27]			
Cmax	Across all 3 cohorts: **0.67 (0.58–0.77)**		
$AUC_{0\text{-last}}$	Across all 3 cohorts: 0.84 (0.76–0.92)		
Jext 0.3 mg compared to 0.3 mg IM by needle/syringe[28–30]			
Cmax	1.07 (0.84–1.37)	0.78 (0.54–1.13)	1.13 (0.81–1.58)
	Across all 3 cohorts: 0.98 (0.82–1.18)		
$AUC_{0\text{-30}}$	1.16 (0.86–1.58)	0.85 (0.59–1.25)	0.66 (0.39–1.12)
	Across all 3 cohorts: 0.87 (0.61–0.98)		
$AUC_{0\text{-last}}$	1.23 (1.04–1.46)	0.99 (0.82–1.19)	**1.92 (1.58–2.33)**
	Across all 3 cohorts: 1.08 (0.64–1.83)		
Epipen 0.3 mg compared to 0.3 mg IM by needle/syringe[22]			
Cmax	NR	NR	NR
	Across all 3 cohorts: 1.40 (1.18–1.65)		
$AUC_{0\text{-30}}$	**2.09 (1.48–2.96)**	1.64 (0.99–2.73)	**2.90 (1.55–5.43)**
	Across all 3 cohorts: **2.13 (1.59–2.85)**		
$AUC_{0\text{-last}}$	NR	NR	NR
	Across all 3 cohorts: 1.13 (0.99–1.30)		

Note: Data are ratios of geometric least square mean with 90% confidence intervals. The accepted interval of bioequivalence is 0.8–1.25. If the 90% CI of the ratio of log (Cmax, AUC) is completely within the range 0.8–1.25, this implies that the two treatments are not statistically 'different' from each other. If the 90% CI of the ratio is completely outside the 0.8–1.25 range, this implies the two interventions are not bioequivalent. Non-bioequivalence is highlighted in bold. NR, not reported. Where the 90% confidence interval is 1.25, the device gives a superior Cmax or AUC than the comparator one.

profile, with a second delayed peak at about 40 min after injection for Epipen and Jext, and about 60 min for Emerade. The difference was most apparent in those with higher STMD (Table 3). While there has not been a direct comparison with Anapen, Duvauchelle et al.[21] demonstrated that Anapen (also a syringe-based device) results in a higher Cmax than manual injection of an equivalent dose by needle/syringe (Figure 3).

Somewhat curiously, while the PK profile for Epipen was very consistent in both Worm et al.[22] and the study funded by the manufacturer of Emerade,[27] Worm et al also reported a somewhat delayed peak in adrenaline when given by needle/syringe. These data are in stark contrast to other studies which all demonstrated rapid absorption of adrenaline when given both by needle/syringe.[17–19,21,27] Simons et al also demonstrated no difference in Tmax for adrenaline given (first-generation) Epipen compared with needle/syringe.[18] In the study by Worm et al.[22] participants in the low STMD cohort had IM injection using a narrower-bore needle (which might impact on PK profile); however, the needles used in the other participants (22G or 23G) were similar to that in the Epipen (22G); therefore, this does not explain the delay in peak adrenaline seen with needle/syringe. One potential explanation is that the analysis by Worm et al failed to consider the biphasic profile of absorption usually seen with adrenaline in these types of studies (i.e., reflected in the high coefficient of variation for Tmax reported for Epipen of 102%).

In summary, differences in PK profile are apparent between different AAI, which are more obvious in individuals with increasing STMD. Adrenaline absorption seems to be most delayed by an increasing STMD for Emerade compared to Epipen, with Jext being intermediate. Unfortunately, the current data do not allow an assessment of the relative roles of needle length versus device mechanism, in understanding why Anapen and Epipen both seem to cause a rapid peak in adrenaline absorption while that seen for Emerade is more delayed.

6 | LOCATION OF INJECTION

Simons et al.[18] compared the PK profiles achieved with first-generation Epipen and adrenaline via needle and syringe at different locations. Surprisingly, IM injection into the deltoid muscle in the arm was not only lower than into the mid-thigh, it was

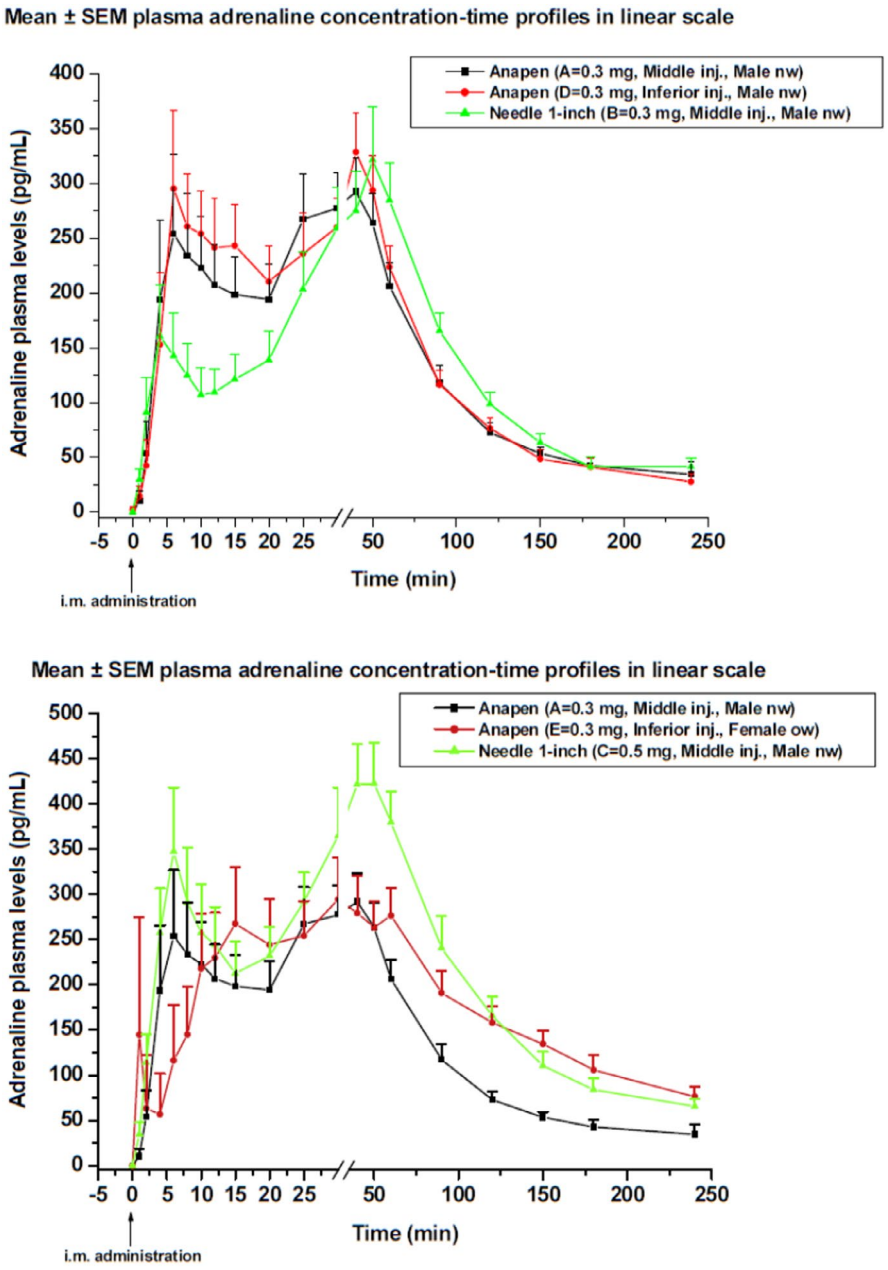

FIGURE 3 Pharmacokinetics of Anapen adrenaline autoinjector. Figures show plasma adrenaline concentrations with different anapens and needle-syringe combinations. Reproduced with permission from Duvauchelle 2018[21]

apparently almost absent, with minimal absorption which seems counter-intuitive given the use of IM injection into the deltoid as the preferred injection site for many medications (Table 1).[18] The authors do not give any explanation for this observation, and the data are challenging to interpret.

A number of studies have compared injection at the mid- versus distal anterolateral thigh. For Epipen, administration at the distal thigh gave a slightly lower peak plasma concentration than at the mid-thigh, although the difference did not imply lack of bioequivalence (0.41 vs. 0.52 ng/ml; geometric mean ratio, 0.77; 90% CI 0.63%–0.94%).[22] The time-to-peak concentration was also slightly longer (25 vs. 20 min).[22] Duvauchelle et al.[21] reported no significant difference in PK profile between mid-thigh versus distal injection with Anapen (Table 1, Figure 3). Thus, no clear conclusion can be drawn as to the most optimal site of injection in the thigh, although distal injection in individuals with a lower STMD may risk an intraosseous injection.

7 | IMPACT OF DOSE

There are data comparing different dosages for the first-generation Epipen and the Emerade. In a very small study of 12 children randomized to a 0.15 mg or 0.3 mg administered with the first-generation Epipen, there was no difference in plasma adrenaline concentration between the two groups (Table 1), although more adverse events were reported with the higher dose.[19] Two studies compared Emerade 0.3 mg versus 0.5 mg in a crossover study design, one in teenagers[23] and the other in adults.[27] In both studies, the 0.5 mg dose achieved a far higher Cmax and AUC compared with 0.3 mg

(Table 1). Patel et al.[23] further reported no significant increase in adverse events (other than mild tremor) with the 0.5 mg dose. The latter data are also consistent with Duvauchelle et al.[21] who demonstrated a higher Cmax with 0.5 mg compared to 0.3 mg adrenaline (injected by needle/syringe), with time-to-peak Cmax around 5 min for both. However, while a higher adrenaline dose results in higher Cmax, we do not know the optimal adrenaline concentration required to treat anaphylaxis.

8 | DISCUSSION

8.1 | Summary

We now have access to pharmacokinetic data for all the currently available AAI. These data demonstrate that it takes at least 5–10 min to achieve early peak plasma concentrations for most devices. The AAI device seems to be the most important factors in terms of pharmacokinetics, with different adrenaline plasma concentrations seen with different devices. The degree to which this is dependent on needle length is challenging to unpick. Another potentially important factor is the force and speed at which adrenaline is injected. This varies by device, with forces likely to be higher for cartridge-based (Epipen, Jext) compared to Anapen, a syringe-based system which uses a lower-tension spring.[34] It is unclear how the force of injection for Emerade (a syringe-based device with a high-tension spring) compares to cartridge-based devices. The available PK data suggest that absorption of adrenaline following percutaneous injection into the mid-thigh in patients with higher STMD is delayed with some autoinjectors, with a lower initial peak concentration and a longer time-to-maximum concentration. This does not appear to be related to the depth of injection.

8.2 | Limitations of current pharmacokinetic data

Although PK data are available, the most helpful study comparing three different devices is unpublished.[27] There is large intra- and inter-subject variability in PK outcomes, which reinforce the importance of using a crossover design to minimize this issue. The published studies are also relatively small and so have limited statistical power for comparisons between subgroups; many do not include appropriate statistical assessments for bioequivalence. Many studies evaluated the PK profile on the basis of uniphasic rather than biphasic absorption kinetics for IM adrenaline: this further confounds analysis and can be potentially misleading (e.g., the assertion by Worm et al that a manual IM injection of adrenaline takes almost 60 min to reach peak absorption[22]). Finally, most have enrolled healthy adults who are not at increased risk of anaphylaxis. This means that we have to assume that absorption of adrenaline is similar in individuals who are at risk of anaphylaxis (which is likely) or during an acute anaphylaxis episode—this may not be a valid assumption, since blood supply to muscle and subcutaneous tissues may be different during acute reactions.

8.3 | Implications for managing anaphylaxis and conclusions

We recommend the IM route as there is an absence of data demonstrating that subcutaneous injection is at least bioequivalent to IM injection. Given that the first peak in adrenaline absorption occurs at least 5–10 min after AAI administration and potentially much longer in individuals with high STMDs, it does not make sense to repeat a dose until a reassessment of the patient after 5–10 min. This, however, assumes that an adequate dose was given in the first place: according to all international guidelines, the recommended dose of IM adrenaline in older children and adults is 0.5 mg; thus, a dose of 0.3 mg given by AAI may be inadequate and should be repeated after 5–10 min in the absence of resolution of symptoms.

Arguably, the biggest limitation is that plasma adrenaline is used as a surrogate for treatment response: we do not know the optimal plasma adrenaline range we should be targeting to treat an episode of anaphylaxis. To address this, data are needed from pharmacodynamic studies undertaken on patients *during* anaphylaxis, to assess how treatment response relates to plasma adrenaline.[35] It may be that the optimal dose range varies according to the clinical status of the patient, with higher concentrations needed in severe anaphylaxis.[4] Further work is needed to better understand the relative importance of needle length versus device mechanism/force of injection on PK outcomes, and the mechanism by which patients with a higher STMD appear to have a lower and more delayed peak in plasma adrenaline. This is an important knowledge gap, which may be helpful in improving the design of the next generation of adrenaline autoinjectors.

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

All authors participated in drafting the article and revising it critically and have approved the final version.

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