Bioavailability and Cardiovascular Effects of Adrenaline Administered by Anapen® 500µg Auto-injector in Healthy Volunteers

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Abstract

Background: Anaphylaxis guidelines recommend intramuscular adrenaline, commonly administered using an auto-injector device, as cornerstone therapy.

Objective: To evaluate the pharmacokinetics and the pharmacodynamic cardiovascular profile after a single adrenaline injection using an Anapen® auto-injector in healthy normal weight males and otherwise healthy, overweight or obese females.

Methods: In this exploratory open-label, single-center study, 54 healthy volunteers aged 18–50 years received a single 500 µg adrenaline injection (Anapen® auto-injector), in the thigh (antero-lateral middle third [males] or antero-inferior third [females]). Depot depth was measured by ultrasonography, plasma adrenaline levels were evaluated by liquid chromatography–tandem mass spectrometry, and heart rate (HR) was measured using an ECG Holter monitor.

Results: Ultrasonography showed that 82.4% of normal weight males received intramuscular injections, whilst all overweight and obese females received subcutaneous injections. Anapen® injection produced rapid increases in circulating adrenaline levels (within 15 min post-injection, all subjects) accompanied by significant increases in systolic blood pressure (SBP) and HR. Second peak plasma adrenaline concentrations (C_{max2}) were reduced and time to C_{max2} increased in overweight and obese females compared with normal weight males, while $AUC_{(0-240)}$ was increased in overweight and obese females. Obese females had reduced maximal SBP values compared with normal weight males or overweight females; overweight and obese females had markedly different HR time courses compared with normal weight males.

Conclusion: A 500 µg adrenaline injection using the Anapen® device produced rapid pharmacokinetic and pharmacodynamic changes in normal weight, overweight and obese subjects, irrespective of intramuscular or subcutaneous injection, and was well tolerated.

Key words: Adrenaline; Anapen®; Anaphylaxis; Auto-injector; Cardiovascular responses; Pharmacodynamic; Pharmacokinetic

Introduction

Anaphylaxis is a serious, potentially fatal, allergic reaction commonly triggered by food, insect venom or medicinal drugs.[1–5] Guidelines recommend intramuscular adrenaline as first-line therapy for anaphylaxis.[6–9] An early randomized controlled pharmacokinetic (PK) trial in healthy volunteer adults demonstrated that intramuscular injection of adrenaline into the thigh was the preferred route of administration. This was achieved using either an auto-injector or ampoule-based injection using a needle and syringe.[10] Adrenaline administration by auto-injector is the preferred method of treating anaphylaxis in the community, particularly in individuals who are at-risk for anaphylaxis.[11,12] However, after a procedure following Article 31, the European Medicines Agency requested all companies marketing adrenaline auto-injectors in the European Union to implement PK/pharmacodynamic (PD) clinical studies in order to assess the relevance of their devices.

A recent PK and PD study which compared the Anapen® auto-injector device (10.5 mm needle length; Bioprojet Pharma, France) versus a prefilled syringe with a 25.4 mm needle to administer adrenaline to healthy adult volunteers, at the most common dosage (300 μg), showed that needle length and intramuscular injection are not absolute requirements for efficacy; it also demonstrated the biphasic PK and PD responses and underlined the importance of a precocious first peak in this life-threatening condition.[13] Comparison of PK profiles in normal weight men and overweight women treated with Anapen® showed that the magnitude of the first peak of circulating adrenaline was similar, despite the injection being subcutaneous in the latter group.[13] However, the current adrenaline dose of 300 μg may not suffice for patients with a large body mass index (BMI) which may require a larger dose for adequate cardiovascular response.

In this study, we compare the local injection targeting, pharmacokinetic (PK), pharmacodynamic (PD) cardiovascular and tolerance profiles of adrenaline after a single 500 µg injection in the thigh using an Anapen® auto-injector in three different populations: normal healthy male volunteers, and otherwise healthy, overweight or obese female volunteers.

Methods

Design

This was an open-label, single-center, one-period study (EudraCT number: 2016-000269-22).

Ethical approval

Study approval was given by an independent Ethics Committee (CPP) of Sud-Est IV, Lyon, France and the French Regulatory Authority - Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM). The study was performed in accordance with Good Clinical Practice and the ethical principles stated in the Declaration of Helsinki.[14]

Inclusion and exclusion criteria

Male or female healthy volunteers aged 18 to 50 years who were non-smokers or light smokers (<5 cigarettes per day) were eligible. The study recruited healthy male normal weight volunteers with a BMI of 18–26 kg/m² and otherwise healthy, overweight (BMI >26–34 kg/m²) and obese (BMI >34–42 kg/m²) female volunteers. Each participant provided written informed consent.

Main exclusion criteria were: clinically significant acute or chronic disease, including known or suspected HIV (HIV 1 or 2 antibodies), HBV (hepatitis B surface antigen (HbsAg)-positive) or HCV (HCV antibodies) infection; a history of allergy, allergic skin rash, asthma, intolerance, sensitivity or photosensitivity to any drug; clinically significant abnormality following review of pre-study laboratory tests, vital signs, full physical examination, cardiac echocardiography and cardiac stress test for males aged >35 years and females aged >40 years, and electrocardiogram (ECG); pregnancy; suspected alcohol (>14 units of alcohol per week) or drug abuse (positive urine drug screening test for opiates, cocaine, amphetamine, barbiturates, cannabis, benzodiazepines); excessive caffeine consumption (>8 cups, daily); surgery or blood donation within 12 weeks prior to the start of the study; taken any prescribed or over the counter drug (including antacids), with the exception of oral contraceptives, menopausal substitutive treatment, and paracetamol (up to 3 g per day) within 2 weeks prior to treatment.

Treatment

For 48 h preceding treatment and up to the end of study, subjects abstained from smoking and drinking alcohol, coffee, tea or beverages containing methylxanthines (i.e. theophylline, caffeine or theobromine). Prior to administration, subjects fasted overnight for a minimum of 10 h.

A single injection of adrenaline (500 µg) using the Anapen® auto-injector device was administered into the antero-lateral middle third of the thigh (male participants) or the antero-inferior third of the thigh (females).

Objectives

The primary objective was to evaluate the PK and the PD cardiovascular profile of adrenaline after a single 500 µg injection in the thigh using an Anapen® auto-injector in three different populations: normal healthy male volunteers, and otherwise healthy, overweight or obese female volunteers. Secondary objectives were to assess the local and general tolerability of adrenaline after a single 500 µg injection in the thigh using an Anapen® auto-injector in the three different populations, and to document the possibility of using ultrasound imaging to determine the injection depth.

Ultrasonography

Ultrasound imaging of the injection site was performed pre-and post-injection to measure the distance between the upper skin layer and the *fascia lata* of the muscle and depth of drug depot, respectively.

Pharmacokinetics (PK)

Blood samples were collected at −30, −20, −10, 1, 2, 4, 6, 8, 10, 12, 15, 20, 25, 30, 40, 50, 60, 90, 120, 150, 180 and 240 min post-dosing. Plasma adrenaline concentrations were measured using a validated liquid chromatography–tandem mass spectrometry (LC–MS/MS) method. PK parameters were derived using Phoenix WinNonlin software, v6.3 (Pharsight Corporation, Mountain View, California, USA) using non-compartmental analysis. PK parameters for adrenaline determined were: C_{max1} and C_{max2} (first and second peak plasma adrenaline concentrations, respectively); t_{max1} and t_{max2} (time to C_{max1} and C_{max2}, respectively), and area under the curve (AUC) parameters, $AUC_{0\text{-}20}$, and $AUC_{0\text{-}240}$.

Pharmacodynamics (PD)

Systolic blood pressure (SBP), pulse rate and Holter ECG-calculated heart rate (HR) were recorded. Mean heart rate was evaluated by 1 min time windows from 30 min pre-dose to 2 h post-dose using a 12-lead 200 Hz Holter ECG. For SBP, PD parameters determined were: $E_{max0-20}$, $E_{max20-60}$, $E_{max60-240}$ (post-dose maximum changes from baseline effect); $t_{Emax0-20}$, $t_{Emax20-60}$, $t_{Emax60-240}$ (time to E_{max}); area under the effect curve (AUEC) parameters - $AUEC_{0-20}$, $AUEC_{20-60}$, $AUEC_{60-240}$ and the proportion of responders. For HR, the same PD parameters were determined except $E_{max60-120}$, $t_{Emax60-120}$ and $AUEC_{60-120}$ which replaced the corresponding 60-240 min parameters.

Safety

The incidence of adverse events (AEs) and changes in physical examination, vital signs (blood pressure and HR), body weight, ECG, continuous cardiac rhythm monitoring and clinical laboratory tests between screening and the end of study were recorded.

Statistical methods

All statistical analyses were conducted using SAS® version 9.4. Categorical data were described using frequency and percentages, and continuous variables were described using the mean, standard deviation (SD), median, minimum, maximum, and number of observations; and 95% confidence intervals (CI) were calculated for changes from baseline.

E_{max} values calculated for SBP and HR, were analyzed using an analysis of covariance (ANCOVA) model using baseline value as a covariate and group as a fixed effect. Wilcoxon rank sum tests were used for paired comparisons of variables. The proportion of responders defined by an increase in SBP ≥10 mmHg or an increase in HR ≥10 bpm on one or more occasion, was analyzed using a logistic model including group as a fixed effect.

PK and PD results were correlated using a linear model including age as a covariate for SBP vs. C_{max} and a sigmoidal saturable E_{max} model for HR *vs.* C_{max}.

Results

A total of 54 healthy subjects equally divided into three groups of 18 were enrolled in the study: male subjects with a mean (SD) age of 26.1 (4.3) years and a mean (SD) BMI of 23.3 (2.1) kg/m^2 (range 19.3 to 26 kg/m^2; Group 1); female subjects aged 30.3 (5.0) years with a mean (SD) BMI of 29.9 (2.1) kg/m^2 (range 26.7–33.3 kg/m^2; Group 2); and female subjects aged 32.8 (7.7) years with a mean (SD) BMI of 36.8 (2.1) (range 34.1–41.7 kg/m^2; Group 3) (Table 1).

Ultrasonography

The distance between skin and muscle (considered to correspond to skin thickness) and the depth of depot are summarized by group, in Table 2. Mean skin thickness was 0.60 cm in Group 1 (normal weight males) but increased in obese subjects with mean values of 2.1 cm and 2.5 cm in Groups 2 (overweight females) and 3 (obese females), respectively. The maximum skin thickness observed was 4 cm.

Overall, most subjects in Group 1 received intramuscular injections shown by a negative mean difference between skin thickness and depth of depot (−0.6) (Table 2). In 14 of 17 evaluable subjects (82.4%), values ranged from −0.47 to −1.14 cm indicating intramuscular injection. However, in three subjects (17.6%) who had values between -0.09 (borderline) and 0.12 cm, injections were subcutaneous. A fluid depot was not visible in one Group 1 subject.

Mean differences between skin thickness and depth of depot in Groups 2 and Group 3 were 0.6 and 1.1, respectively, indicating subcutaneous injections (Table 2). In Group 2, values

varied from -0.04 (borderline) to 1.58 cm, whereas the range in Group 3 was from 0.29 to 2.20 cm. A fluid depot was not visible in one Group 3 subject.

Pharmacokinetics

Baseline measurement of plasma adrenaline concentrations were conducted at three time points 10 min apart (30, 20 and 10 min before injection). Most subjects had adrenaline concentrations below the limit of quantitation (39.1 pg/mL), but 8 subjects (6 in Group 1, 1 each in Groups 2 and 3) had quantifiable plasma adrenaline which was <10% of the C_{max} in 7 subjects but more than 27% of C_{max} in one subject (baseline value 10 min before injection of 115.8 pg/mL). Consequently, PK analysis was performed on baseline-corrected concentration values for all subjects.

Adrenaline injection produced biphasic increases in mean plasma adrenaline concentrations over time in each group (Figure 1). In all groups, the first peak occurred within 15 minutes with median t_{max1} values for Groups 1, 2 and 3 of 0.23 (13.8 min), 0.23 (13.8 min) and 0.25h (15.0 min), respectively, which did not differ significantly (Table 3). The rank order of the timing of the second peak was the same with normal weight males (Group 1) having a median t_{max2} of 0.67h, equal with 0.67h in overweight females (Group 2) compared with 0.83h in obese females (Group 3) (Table 3). These equated to 40.2, 40.2 and 49.8 min, respectively from the time of injection (T0).

Except in Group 2, C_{max2} values were higher than, or comparable to, the corresponding C_{max1} values (Table 3) as illustrated in the plasma adrenaline concentration time course graphs in Figure 1. In both overweight (Group 2) and obese (Group 3) females the second peak was broader than that of normal weight males (Group 1), and mean C_{max2} values lower in Groups 2 (642.20 pg/mL), and 3 (723.66 pg/mL), compared with Group 1 (809.03 pg/mL). Mean

$AUC_{0\text{-}20}$ values were comparable in Groups 1, 2 and 3: 117.08, 123.48, and 110.30 h.pg/mL, respectively; whereas mean $AUC_{0\text{-}240}$ was higher in overweight (1190.34 h.pg/mL) and obese females (1454.82 h.pg/mL) compared with normal weight males (965.21 h.pg/mL) (Table 3). Adrenaline plasma concentrations in all groups did not return to basal levels within the 240 min time period of the study (Figure 1).

Pharmacodynamics

Time courses of mean change from baseline in SBP were comparable between groups with a rapid increase within the first few minutes post-injection followed by a decrease and a secondary increase that lasted from about 6 min to 60 min post-dose (Figure 2). Maximum mean changes in SBP were observed at approximately 40 min in Group 1 (+10.4 mmHg), 20 min in Group 2 (+11 mmHg) and 60 min in Group 3 (+6.8 mmHg).

Time courses of mean changes from baseline in HR showed an increase from around 1 min in all groups, but differences were apparent in profiles between normal weight males *vs.* overweight or obese females (Figure 3). In Group 1, three main peaks (with fluctuations within each peak) were observed, but in Groups 2 and 3 there was less discrimination of peaks with effects prolonged, which could be linked to the higher bioavailability and AUC.

In all groups, adrenaline injection significantly increased SBP (Figure 2) and HR (Figure 3) from baseline irrespective of time interval (0–20, 20–60 or 60–240 min) ($p < 0.01$).

Pairwise comparisons of groups showed no significant differences for SBP- or HR- derived PD parameters E_{max} or t_{Emax} which are displayed in Table 4.

PK/PD analysis showed that SBP and HR changes are directly related to circulating adrenaline concentrations with significant correlations ($p < 0.01$) irrespective of time interval (0-20, 20-60 or 60-240).

However, for Groups 2 and 3, a delay was observed from maximum mean C_{max} (40–60 min post injection) to maximum change of HR (around 100 min).

The proportion of responders (defined as increases in SBP by ≥10 mmHg or HR by ≥10 bpm) was ≥88.9% in each group and varied depending on group and time interval. The response rates in Group 1, for 0-20, 20-60 and 60-240 min were 94.4% (n = 17), 100% (n = 18) and 100% (n = 18), respectively. Respective response rates in Group 2, were 100% (n = 18), 100% (n = 18) and 88.9% (n = 16); and in Group 3 were 88.9% (n = 16), 94.4% (n = 17) and 100% (n = 18).

Safety

A total of 12 TEAEs were reported by nine subjects (16.7%) treated with 500 µg adrenaline using the Anapen® device. All TEAEs were of mild (5) or moderate (7) intensity. No AEs of severe intensity nor serious adverse events (SAE) were reported during the study.

All TEAEs were considered related to study product administration. The most frequent TEAEs were nervous system disorders consisting of headache and tremor. These effects are known to occur in some people after adrenaline administration.

Injection site reactions were common: skin whitening was observed in one or more occasion in 29 subjects (53.7%), swelling was observed in 2 subjects (3.7%) and erythema in 1 subject (1.9%). Skin whitening is most likely related to localized vasoconstriction while swelling is probably caused by the injection itself.

Some pre-existing individual abnormalities were recorded on laboratory parameters and ECG parameters. However, all these abnormalities were considered as non-clinically significant and reported in all groups.

Discussion

This study investigated the PK and PD of a single 500 µg adrenaline injection using the Anapen® auto-injector in healthy normal weight male and otherwise normal, overweight and obese female volunteers. Ultrasound scanning showed that most (89%) normal weight male subjects received intramuscular injections whereas in all overweight or obese female subjects, injections were subcutaneous. Despite differences in the location of the adrenaline depot the first peak of plasma adrenaline was still observed during the 0–20 min window: t_{max1} was within 15 min post-injection in each group and C_{max1} values were comparable in the three groups. This is particularly important for counteracting the initial symptoms of anaphylactic shock i.e. the fall in BP and heart depression. Increases in plasma adrenaline levels were accompanied by rapid increases in SBP and HR.

Marked differences in PK and PD between normal weight male *versus* overweight or obese female subjects were observed during the 4 h time course of the study with differences in the location of the adrenaline depot likely to have a significant impact on results. Discrepant results included reduced C_{max2} and increased t_{max2} (within the 20–240 min window) in overweight and obese female subjects compared with normal weight male subjects, reduced SBP E_{max} in obese female subjects compared with normal weight male or overweight female subjects; and markedly different HR time courses in overweight and obese females compared with normal weight males.

Comparison of the current PK results with a PK study using Anapen®300 in healthy normal weight male and overweight female volunteers,[13] showed that increasing the adrenaline dose from 300 to 500 μg (1.67-fold) produced increases in C_{max1}, $C_{max2,}$ AUC_{0-20} and AUC_{0-240} by 1.70-, 2.21-, 1.69- and 2.10-fold, respectively, in normal weight male subjects; and by 1.51-, 1.79-, 2.21- and 1.76-fold, respectively, in overweight females. Results in normal weight males showed that use of Anapen® 500 (current study) in comparison with injection of 500 μg adrenaline using a 1-inch (25 mm) needle (Group C; Duvauchelle et al.[13]) increased C_{max1}, $C_{max2,}$ AUC_{0-20} and AUC_{0-240} by 1.6-, 1.5-, 1.5- and 1.2-fold, respectively. These results are consistent with previous results in normal weight males which showed significantly improved bioavailability (i.e. increased maximum adrenaline concentration [C_{max1}, C_{max2}] and AUC [AUC_{0-20} and AUC_{0-240}] with Anapen® 300 compared with 300 μg adrenaline delivery with a prefilled syringe and a 1-inch needle).[13]

In common with this study, the magnitude of the first peak (C_{max1}) following injection with 300 μg adrenaline in normal weight men and overweight women was similar.[13] The present study also included obese women, who displayed slightly lower mean C_{max1} values than normal weight men and overweight women although there was considerable variance in the groups.

Tolerability after 500 μg adrenaline injection using the Anapen® device was good, with headache and tremor which were mild or moderate in intensity, being the most commonly reported TEAEs. These effects are known following adrenaline administration.[15] Compared with the 300 μg adrenaline injection there was a nearly proportional increase in responses that was well tolerated indicating that the dose increase should result in an enhanced efficacy associated with similar tolerance. This pattern should offer a valuable alternative in overweight or obese patients.

The current open-label study has some limitations, with the key limitation being that data obtained in healthy volunteers cannot be readily extrapolated to individuals who are in a stage of anaphylactic shock; however, for the latter, this kind of study is impossible for ethical and practical reasons. In addition, the effects of a single 500 µg adrenaline injection were only evaluated in health normal weight male, and otherwise healthy overweight or obese female, volunteers; thus, the PK and PD cardiovascular effects of adrenaline doses other than 500 µg in other populations cannot be ascertained from the current study.

In conclusion, a single 500 µg adrenaline injection using the Anapen® auto-injector in healthy normal weight male and otherwise normal, overweight and obese female volunteers, produced rapid increases in circulating adrenaline levels which were accompanied by significant increases in SBP and HR. These responses occurred irrespective of whether the injection was intramuscular or subcutaneous and, in all cases, treatment was well tolerated.

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Conflicts of interest

T. Duvauchelle has received consultancy fees from Phaster1 and is employed by Bioprojet. P. Robert is employed by Bioprojet. Y. Donazzolo has received consultancy fees and fees for participation in review activities, and payment for writing/reviewing the manuscript from Eurofins Optimed. S. Loyau and B. Orlandini have received consultancy fees, fees for

participation in review activities, and payment for writing/reviewing the manuscript from PhinC Development. P. Lehert has received consultancy fees from Bioprojet. J.-M- Lecomte and J.-C. Schwartz are employed by, and have stock/stock options in, Bioprojet.

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Tables and Figures

Tables

Table 1 Demographic data in Groups 1–3.

	Group 1 (n=18)	Group 2 (n=18)	Group 3 (n=18)
Sex	Male	Female	Female
Age (years), mean (SD)	26.1 (4.3)	30.3 (5.0)	32.8 (7.7)
Height (cm), mean (SD)	176.9 (6.1)	163.7 (6.6)	164.3 (5.7)
Weight (kg), mean (SD)	72.9 (6.8)	80.3 (8.4)	99.4 (7.5)
BMI (kg/m^2), mean (SD)	23.3 (2.1)	29.9 (2.1)	36.8 (2.1)

All subjects were Caucasian with the exception of 3 individuals: 1 male in Group 1 and 1 female in Group 2 were Black and 1 female in Group 2 was Hispanic.

Table 2. Ultrasonographic measurements of skin-to-muscle distance and depot depth in Groups 1–3.

Group	Skin-to-muscle distance (cm)	Depot depth (cm)	Difference (cm)
Group 1	0.6 (0.2)	1.2 (0.2)	−0.6 (0.4)
Group 2	2.1 (0.5)	1.5 (0.2)	0.6 (0.4)
Group 3	2.5 (0.6)	1.4 (0.2)	1.1 (0.6)

All data are presented as mean (SD); n = 18 for all measurements, except depot depth measurement in Groups 1 and 3 (n = 17)

Table 3. Pharmacokinetic parameters for Groups 1–3 (n = 18 for each group).

Group	**t_{max1*} (h)**	**C_{max1} (pg/mL)**	**t_{max2*} (h)**	**C_{max2} (pg/mL)**	**AUC_{0-20} (h.pg/mL)**	**AUC_{0-240} (h.pg/mL)**
Group 1	0.23	640.28 (486.51)	0.67	809.03 (376.29)	117.08 (78.83)	965.21 (313.90)
Group 2	0.23	665.72 (386.88)	0.67	642.20 (246.58)	123.48 (80.46)	1190.34 (315.44)
Group 3	0.25	569.63 (517.80)	0.83	723.66 (263.79)	110.30 (108.59)	1454.82 (433.91)

Data are presented as mean (SD) unless stated otherwise.

*Median value

t_{max1} and C_{max1} are defined over the first 20 min post-dose interval; t_{max2} and C_{max2} are defined over the 20-240 min post-dose interval

Table 4. Mean (SD) Systolic Blood Pressure (SBP)- and Heart Rate (HR)- derived parameters over three time intervals (0–20, 20–60, and 60–240 min) in Groups 1–3

Time interval (min)	Group	Systolic Blood Pressure			Heart Rate		
		E_{max} (mmHg)	t_{Emax} (min)	AUEC (mmHg.min)	E_{max} (beats)	t_{Emax} (min)	AUEC (beats.min)
0–20	1	16.6 (8.5)	10.5 (7.5)	166.2 (121.4)	20.7 (9.7)	9.1 (5.9)	120.7 (112.4)
	2	14.7 (6.1)	9.0 (6.7)	145.0 (101.8)	19.2 (7.1)	10.1 (5.4)	141.7 (114.3)
	3	11.9 (6.3)	6.2 (6.1)	60.8 (100.2)	17.9 (10.1)	11.3 (5.6)	103.6 (111.2)
20–60	1	17.7 (4.9)	37.2 (13.2)	427.1 (208.3)	22.1 (6.7)	39.2 (10.7)	355.7 (264.3)
	2	14.1 (5.3)	29.4 (10.8)	244.0 (240.2)	19.2 (7.7)	45.4 (12.2)	392.9 (273.0)
	3	11.7 (8.7)	40.0 (17.3)	163.9 (278.7)	18.3 (5.6)	41.6 (13.7)	373.2 (242.5)
60–240	1	12.2 (5.2)	101.7 (67.6)	380.8 (853.4)	21.6 (6.3)	81.1 (18.3)	270.6 (316.9)
	2	11.5 (8.4)	161.7 (72.1)	626.7 (987.5)	29.0 (14.1)	87.1 (18.9)	691.8 (485.9)
	3	13.1 (8.4)	118.3 (70.9)	448.3 (1021.1)	25.2 (7.2)	89.2 (19.9)	690.3 (425.8)

E_{max} data represent changes(SD) from baseline

Figures

Figure 1. Time courses of mean adrenaline plasma concentrations after administration of 500 µg adrenaline in Groups 1–3

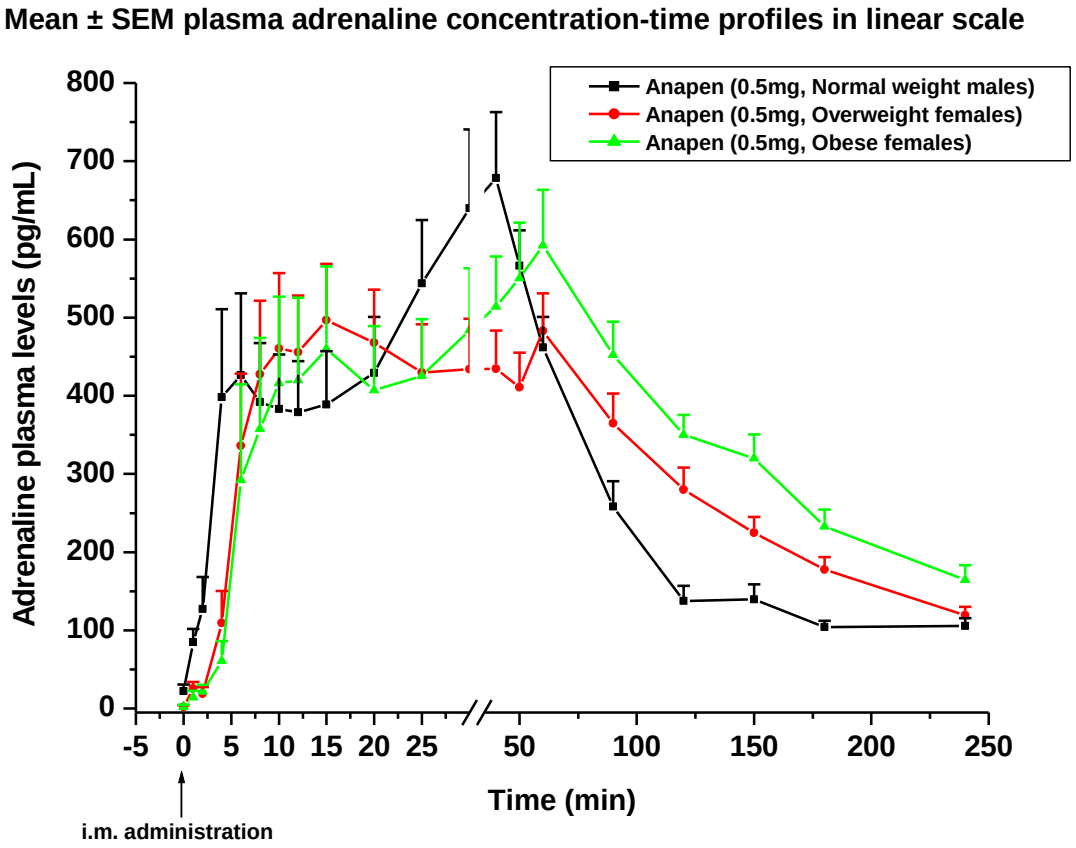

Figure 2. Time courses of mean change from baseline in systolic blood pressure (SBP) in Groups 1–3

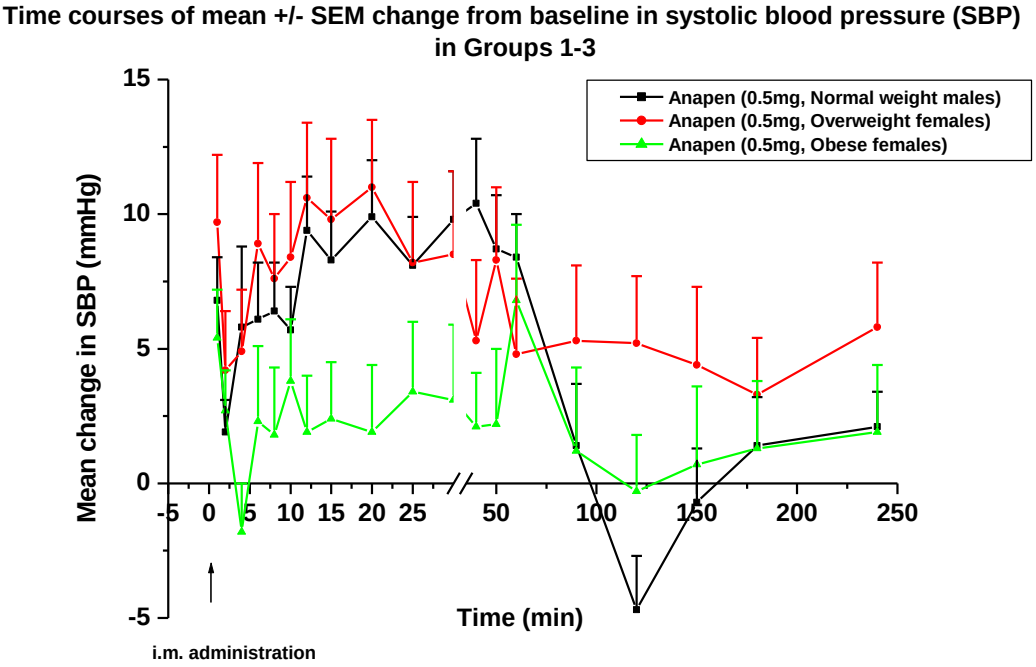

Figure 3. Time courses of mean change from baseline in heart rate (HR) in Groups 1–3