Original Article

Bioavailability and Cardiovascular Effects of Adrenaline Administered by Anapen Autoinjector in Healthy Volunteers

Thierry Duvauchelle, MD[a], Philippe Robert, PhD[b], Yves Donazzolo, MD[c], Sabrina Loyau, PharmD[d], Bernard Orlandini, MSc[d], Philippe Lehert, PhD[e,f], Jeanne-Marie Lecomte, PhD[a], and Jean-Charles Schwartz, PhD[a]

Paris, Saint Gregoire, Gières, and Massy, France; Louvain, Belgium; and Melbourne, Victoria, Australia

What is already known about this topic? Adrenaline autoinjectors used in anaphylaxis should have a sufficient needle length to reach the muscle. Their performance was analyzed using a novel combination of ultrasonography, adrenaline plasma level assays, and cardiovascular responses in human volunteers.

What does this article add to our knowledge? Subcutaneous as well as intramuscular adrenaline, delivered using an autoinjector with a relatively short needle, may ensure optimal bioavailability and cardiovascular response, even in overweight women. The analysis of early bioavailability parameters and cardiovascular response is necessary to assess the speed of action of the devices.

How does this study impact current management guidelines? The prediction of adrenaline autoinjector efficacy in anaphylaxis should be based on the combined assessment of ultrasonographic depot localization, the analysis of biphasic and parallel patterns of plasma adrenaline levels, and the cardiovascular responses in various categories of healthy volunteers.

BACKGROUND: The administration of adrenaline is a life-saving intervention for anaphylactic reactions. However, it has been questioned whether the needle length of the autoinjectors is sufficient to achieve genuine intramuscular delivery and optimal bioavailability.

OBJECTIVE: To assess the adequacy of Anapen, which has a relatively short needle length (10.5 mm), through a comparison of the depot localization, plasma pharmacokinetics, and cardiovascular responses of adrenaline delivered via Anapen versus a prefilled syringe with a 25.4-mm needle, which is generally used for intramuscular injections.

METHODS: This randomized, open-label, crossover study compared the impact of adrenaline administration at 2 sites in the thigh of 18 normal weight male volunteers, using either Anapen or the prefilled syringe; in addition, we studied the treatment of 12 overweight women with Anapen. The depot depth was measured by ultrasonography, plasma adrenaline level was evaluated by ultra performance liquid chromatography-mass spectrometry (UPLC-MS), and heart rates were measured using a Holter monitor.

RESULTS: Intramuscular injections were given with both devices at both thigh sites in nonobese men, but not in overweight women. Adrenaline levels showed a double peak, with parallel changes in the heart rate. The first peak, of potential vital importance in anaphylaxis treatment, occurred at approximately 10 minutes postinjection, with maximum concentration and area under the curve significantly higher with Anapen than with prefilled syringes; the magnitude of the second peak did not differ among the various conditions. Unexpectedly, in overweight women treated with Anapen, the magnitude of the first peak was similar to that observed in men, despite the injection being subcutaneous, and the overall bioavailability was enhanced.

CONCLUSIONS: Needle length and intramuscular injection are not absolute requirements for autoinjector efficacy, but the monitoring of injection location, biphasic adrenaline levels, and cardiovascular responses is important for the assessment of their therapeutic relevance in anaphylaxis. **(J Allergy Clin Immunol Pract 2017;■:■-■)**

[a]Bioprojet Pharma, Paris, France
[b]Bioprojet Biotech, Saint Gregoire, France
[c]Eurofins Optimed, Gières, France
[d]PhinC Development, Massy, France
[e]Faculty of Economics, University of Louvain, Louvain, Belgium
[f]Faculty of Medicine, University of Melbourne, Melbourne, Victoria, Australia

This work was funded by Bioprojet.

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.

Received for publication May 25, 2017; revised September 19, 2017; accepted for publication September 28, 2017.

Available online ■■

Corresponding author: Thierry Duvauchelle, MD, Bioprojet Pharma, 9 rue Rameau, 75002 Paris, France. E-mail: thierry.duvauchelle@bioprojet.com.

2213-2198

https://doi.org/10.1016/j.jaip.2017.09.021

Abbreviations used
AUC- Area under the curve
BMI- Body mass index
C_{max}- *Maximum concentration*
E_{max}- *Maximum effect*
HR- Heart rate
PK- Pharmacokinetic
SBP- Systolic blood pressure
T_{max}- *Time at the* C_{max}

Key words: *Anapen; Autoinjectors; Adrenaline pharmacokinetics; Anaphylaxis; Cardiovascular responses*

Anaphylaxis is a serious allergic reaction that occurs suddenly and requires immediate treatment because it may be fatal.[1-3] Prompt adrenaline injection is widely recognized as the primary medical therapy for this life-threatening condition.[4-8] Adrenaline decreases the release of histamine and other inflammatory mediators from mast cells and antagonizes all major symptoms of anaphylactic shock: it increases the heart rate (HR) and myocardial contractility (through β1-adrenoceptors), enhances peripheral vascular resistance (through α1-adrenoceptors), and induces bronchodilation with increased oxygen absorption (β2-adrenoceptors). Adrenaline has a very low oral bioavailability and intravenous self-administration is not easy, particularly in an emergency. Therefore, prompt intramuscular self-injection of adrenaline is recommended as first-line treatment for serious hypersensitivity reactions. However, individuals are often reluctant to use a syringe and expect difficulties in executing intramuscular injections. Thus, there is a medical need for a safe and easy-to-use autoinjector device to ensure prompt and adequate adrenaline blood levels and cardiovascular responses, at least equivalent to those of standard prefilled syringes. A pioneering pharmacokinetic (PK) study of an autoinjector in volunteers suggested that this was best achieved via intramuscular injection into the thigh.[9]

Anapen, a pen applicator marketed by Bioprojet (Paris, France), provides a dose of 0.3 mg adrenaline through a syringe and a 10.5 mm, 27G × 1/2-in needle. Although it has been used in Europe since 2003 for adrenaline delivery in anaphylactic shock, with an apparently good safety record, no clinical trial has yet been administered to check its performance.

Furthermore, the length of its needle, as well as that of autoinjectors with even longer needles, was suggested to be inadequate to achieve intramuscular delivery (and therefore obtain adequate responses), particularly in women or overweight individuals.[10-16]

The European Medicine Agency has recently recommended several measures to better ensure the appropriate patient use of adrenaline autoinjectors for severe allergic reactions and confirmed that intramuscular injection was the preferred route of administration.[17] In addition, the product manufacturers were asked to conduct PK/pharmacodynamics studies to better elucidate how adrenaline penetrates body tissues when administered through an autoinjector.

The aim of our study was to assess the efficacy and safety of Anapen, a device currently in use for urgent adrenaline delivery during anaphylactic shock. Thus, we compared the pharmacokinetics and pharmacodynamics of an injection of 0.3 mg or 0.5 mg adrenaline delivered via a standard syringe equipped with a 1-in (25.4 mm) 25G needle, traditionally used for intramuscular injection, or Anapen, in 2 sites of the thigh in normal weight men or in overweight women. Moreover, as the length of the Anapen needle has been proposed as possibly insufficient to obtain intramuscular delivery,[18,19] the injection depth was assessed by ultrasound imaging and compared with results obtained for syringes equipped with needles of greater length (~2.5-fold longer than that in the Anapen device). The bioavailability of adrenaline was also compared in each test scenario.

METHODS

Design

The trial was conducted according to the principles of Good Clinical Practice and in accordance with the ethical principles of Declaration of Helsinki. The appropriate approval was provided by the Ethics Committee of Lyon (Sud-Est II), France, and the French Drug Agency (Agence Nationale de Sécurité du Médicament et des produits de santé [ANSM], EudraCT-number 2014-004006-15). Written informed consent was obtained from all participants.

This trial was a single-center, randomized, open-label study to investigate the impact of 0.3 mg adrenaline intramuscular administration using various devices in 18 normal weight healthy men (body mass index [BMI], 18-26 kg/m^2) in a crossover manner and in 12 overweight, but otherwise healthy, women (BMI, 26-34 kg/m^2) (Table I).

The adrenaline injections were administered by a nurse under the supervision of the principal investigator. The role of the injection site was assessed in a crossover manner by using Anapen in normal weight men; as summarized in Table II, the injections were administered either in the middle anterolateral third of the thigh ("mid-injection," corresponding to the commercial device notice instructions) (group A) or in the inferior third anterolateral part of the thigh (group D).

To assess the influence of the needle length, the same men also received a "mid-injection" using a prefilled syringe equipped with longer needles (25G × 1-in [25.4 mm] [Reference: Becton Dickinson #300400 and 300600] vs 27G × 1/2-in [10.5 mm] in Anapen) (group B); the group of overweight women (group E) received the injection using the Anapen autoinjector in the inferior anterior third of the thigh.

Finally, in group C, 18 normal weight men were administered 0.5 mg of adrenaline by using a syringe equipped with a 25G × 1-in needle. All subjects were injected while lying down.

For groups A, B, and C, the injection was administered in the external middle third of the anterolateral part of the musculus quadriceps femoris, as per the Anapen information leaflet; that is, the tip of the device was pressed on the skin and the spring released by pressing the button. The middle third was defined by the middle third of the distance between the upper edge of patella and the middle of the inguinal line. The injection was administered strictly on the external anterolateral middle side of this area. For groups B and C, the entire length of the needle was inserted into the muscle, perpendicularly to the skin, with the instruction to expel the syringe content as rapidly as possible (maximum 1-2 seconds), to mimic the injection extent of the autoinjector. Between periods, the investigator was instructed to administer the injection in the same area of the thigh for each volunteer, to decrease possible variabilities associated with different anatomical localizations. Hence, the location of the first injection was marked on the skin for the subsequent treatments.