

Epinephrine absorption in adults: Intramuscular versus subcutaneous injection

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We report a prospective, randomized, blinded, placebo-controlled, 6-way crossover study of intramuscular versus subcutaneous injection of epinephrine in young men. Peak plasma epinephrine concentrations were significantly higher ($P < .01$) after epinephrine was injected intramuscularly into the thigh than after epinephrine was injected intramuscularly or subcutaneously into the upper arm. We recommend intramuscular injection of epinephrine into the thigh as the preferred route and site of injection of this life-saving medication in the initial treatment of anaphylaxis. (*J Allergy Clin Immunol* 2001;108:871-3.)

Key words: Epinephrine, adrenaline, EpiPen, systemic anaphylaxis, anaphylactic shock, acute allergic reaction, adult, intramuscular, subcutaneous

Epinephrine injection is the initial treatment of choice worldwide for systemic anaphylaxis.¹⁻⁶ Since the drug was introduced a century ago, many different authoritative recommendations have been made with regard to its administration in anaphylaxis. These recommendations have been based on descriptive studies, clinical experience, and tradition rather than on experiment. Both the subcutaneous (SC) and the intramuscular (IM) routes of injection are recommended by experts¹⁻⁶; however, the SC route is often recommended exclusively,¹⁻⁴ especially for "mild" reactions. The injection site is usually not specified. There has been no published prospective, randomized, double-blinded, controlled comparative study of the plasma epinephrine concentrations achieved after use of different routes of epinephrine injection or different sites of injection in the treatment of anaphylaxis.

In a randomized, blinded, parallel-group study of children at risk for anaphylaxis, we previously demonstrated

Abbreviations used

IM: Intramuscular(ly)
SC: Subcutaneous(ly)

that peak plasma epinephrine concentrations were achieved significantly faster after IM injection by means of an EpiPen into the thigh (vastus lateralis) than after SC epinephrine injection in the upper arm (deltoid region).⁷ That study led to recommendations for IM injection of epinephrine in both children and adults with anaphylaxis,⁸ though there was no experimental evidence on which to base such a recommendation in adults.

The research that we report here was designed to provide information regarding the optimal route and site of epinephrine injection in adults, in whom we hypothesized that IM injection would be superior to SC injection.

METHODS

We tested this hypothesis in a prospective, randomized, blinded, placebo-controlled, 6-way crossover study in healthy allergic men age 18 to 35 years. The project was approved by the University of Manitoba Research Ethics Board, and each participant gave signed, informed consent before study entry.

Prospective subjects were excluded if they had any history of cardiovascular, thyroid, or central nervous system disorder or if they smoked or used any medications or recreational drugs. Participants were asked to come to the Health Sciences Clinical Research Centre Allergy Laboratory on 6 different mornings. The visits were scheduled at least 1 week apart; each visit lasted 3.5 to 4 hours. One injection was given at each visit. During the course of the study, each participant received 4 injections of epinephrine 0.3 mg (0.3 mL) and 2 injections of saline solution (0.9% NaCl, 0.3 mL) through use of a variety of injection routes and sites. Epinephrine USP 1:1000, 0.3 mg (0.3 mL) was injected either IM into the vastus lateralis muscle or the deltoid muscle or SC in the deltoid region. Epinephrine 0.3 mg (0.3 mL) was injected IM into the vastus lateralis muscle through use of an EpiPen. Saline solution (0.3 mL) was injected IM into the deltoid muscle or SC in the deltoid region. To ensure blinding, all injections were given by a nurse not otherwise involved in the study, and at each visit both the thigh and upper arm sites were covered after the injection.

A detailed description of our study methods has been published previously.⁷ Before each injection, repeated measurements of heart rate and blood pressure were made at 5-minute intervals until baseline values were stable. Plasma epinephrine concentrations were

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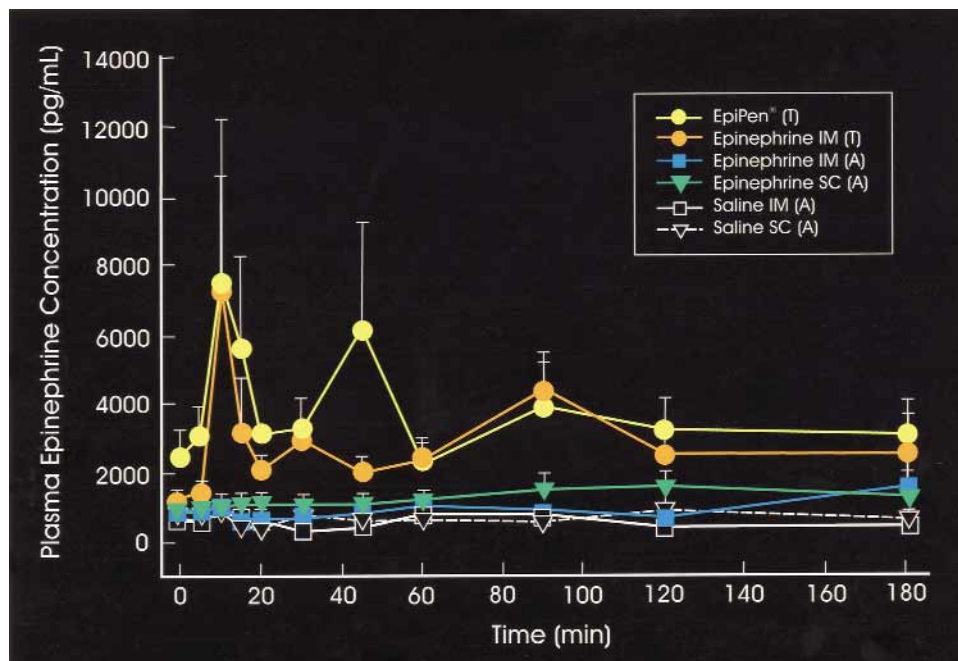


FIG 1. Mean plasma epinephrine concentrations versus time are shown after administration of an identical 0.3-mg (0.3-mL) dose of epinephrine by IM or SC injection in 2 different sites. T, Thigh; A, upper arm. Mean endogenous plasma epinephrine concentrations are shown after IM or SC injection of 0.9% saline solution (0.3 mL) in the upper arm. The plasma epinephrine concentrations shown were calculated by averaging (mean $\pm$ SEM) the epinephrine concentrations at each sampling time for each route and each site of injection.

TABLE I. Mean maximum plasma epinephrine concentrations

Injection route	EpiPen IM	Epinephrine IM	Epinephrine IM	Epinephrine SC	Saline IM	Saline SC
Injection site	Thigh	Thigh	Arm	Arm	Arm	Arm
C_{max} : mean $\pm$ SEM (pg/mL)	12,222* $\pm$ 3,829	9,722* $\pm$ 4,801	1,821 $\pm$ 426	2,877 $\pm$ 567	1,458† $\pm$ 444	1,495† $\pm$ 524

C_{max} (mean $\pm$ SEM) was obtained as follows: We selected the peak plasma epinephrine concentration measured in each participant during each visit (from 5 to 180 minutes after injection, regardless of the time at which the peak concentration occurred). We then calculated the mean peak concentration ($C_{max} \pm$ SEM value) after injection of epinephrine or saline solution by each route and at each site.

IM, Intramuscular; SC, subcutaneous; C_{max} , peak plasma epinephrine concentration.

* $P < .01$ from all arm values.

†Endogenous epinephrine.

monitored before and for 180 minutes after each injection of epinephrine or saline solution. Heart rate and blood pressure were monitored and adverse effects recorded. Plasma samples were frozen at -20°C until analyzed for epinephrine through use of a validated high-performance liquid chromatograph–electrochemical detector method with a limit of quantitation of 5 pg/mL, linear calibration curves over the range 25 to 1000 pg/mL, and a coefficient of variation of 3% at 1000 pg.⁷ Pharmacokinetic and statistical data analyses were performed through use of WinNonLin (Scientific Consulting Inc, Apex, NC) and PC-SAS (SAS Institute Inc, Cary, NC), respectively.

RESULTS

Thirteen men (26 ± 2 years; weight, 85 ± 5 kg [range, 62–114 kg]; body mass index, 36.6 ± 4.6 [range, 20–64]) completed the study. Mean plasma epinephrine concentrations versus time are shown in Fig 1. There was a 9- to 14-fold range in peak plasma epinephrine concentrations

(C_{max}) among doses and routes of injection, a 2-fold variation in body weight, and a 3-fold variation in body mass. Mean C_{max} was significantly higher ($P < .01$) after epinephrine IM injection into the thigh, either from an ampule or an EpiPen, than after epinephrine IM or SC injection into the upper arm, or after saline solution IM or SC injection into the upper arm (Table I).

Mild transient adverse effects were reported after 21 of the 52 epinephrine injections and after 3 of the 26 saline injections, as follows: 7 after EpiPen IM (thigh), 6 after epinephrine IM (thigh), 4 after epinephrine IM (arm), 4 after epinephrine SC (arm), 3 after saline IM (arm), 0 after saline SC (arm). The most common adverse effects were pallor after 13 injections, tremor after 7 injections, and heart pounding after 7 injections. Headache occurred after 3 injections, shivers after 1 injection, and dizziness after 1 injection. Some men experienced several adverse effects concurrently.

DISCUSSION

This study supports the superiority of IM injection of epinephrine into the thigh in adults, either as 0.3 mg (0.3 mL) from an ampule or as 0.3 mg (0.3 mL) from an EpiPen. In contrast, an identical dose of epinephrine injected IM into the deltoid or injected SC in the deltoid region did not result in significant elevation of plasma epinephrine concentrations in comparison with endogenous epinephrine concentrations measured after saline solution injections. The greater absorption of epinephrine from the vastus lateralis muscle in comparison with the deltoid muscle is most likely due to the greater blood flow in the vastus lateralis. The secondary peak in plasma epinephrine concentrations after IM injection of epinephrine by means of the EpiPen, which occurred at 40 minutes, might be due to further absorption of exogenous epinephrine at the injection site after a period of initial vasoconstriction at the site; alternatively, it might be due to rebound endogenous epinephrine release. This phenomenon has been reported in a previous study.⁷

In retrospect, that SC injection of epinephrine has been recommended for almost a century is surprising, given its marked vasoconstrictor effect in the skin, which leads to decreased cutaneous blood flow and obvious blanching lasting up to half an hour at the injection site. Indeed, in other medical settings epinephrine is injected for the specific purpose of delaying the absorption of medications, such as local anesthetics, from injection sites.

Although the plasma and tissue concentrations of epinephrine required for successful treatment of anaphylaxis in human beings are unknown, the differences in peak plasma concentrations that we found after various routes and sites of epinephrine injection not only are statistically significant but also might be clinically relevant in a medical emergency during which every second counts.^{1-6,8,9} In the initial treatment of anaphylaxis, the β_1 -adrenergic effects of epinephrine (vasoconstriction, increased peripheral vascular resistance, and decreased mucosal edema) and the β_2 -adrenergic effects (bronchodilation and decreased release of histamine, tryptase, and other chemical mediators of inflammation from mast cells and basophils) are of primary importance. Epinephrine has a bidirectional effect, and low plasma and tissue concentrations are associated with enhanced release of chemical mediators of inflammation as well as vasodilation and hypotension.¹⁰

Ideally, recommendations for epinephrine administration in anaphylaxis would be based on prospective, ran-

domized, double-blinded, placebo-controlled trials in patients actually experiencing severe acute allergic reactions. Such clinical trials would be unethical, because prompt administration of epinephrine is of critical importance for the survival of a patient with anaphylaxis, which is occasionally fatal despite prompt epinephrine treatment.⁹ Furthermore, such trials would be difficult or impossible to conduct, since most severe acute allergic reactions occur without warning, take place outside of a health care setting, and differ considerably in severity among patients and from one reaction to another in the same patient.

Despite the limitation that this study was not performed during severe acute allergic reactions, our data suggest that in adults, as we previously demonstrated in children,⁷ IM injection of epinephrine into the thigh is the preferred method of administration of this life-saving medication in the initial treatment of anaphylaxis.

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