

Letters

Comparison of the pharmacokinetics between intramuscular and subcutaneous manual epinephrine administration



Epinephrine has been the first-line treatment for severe allergic reactions including anaphylaxis for several decades. Historically, the approved epinephrine injection products by the US Food and Drug Administration (FDA) have been considered clinically comparable, with nearly identical product labeling. However, a growing body of evidence now suggests that there are substantive pharmacokinetic and pharmacodynamic differences among these products.^{1–4}

A series of pharmacokinetic studies compliant with Good Clinical Practice was conducted to evaluate the comparative bioavailability of a novel intranasal epinephrine spray against epinephrine injection products. As part of these studies, we evaluated the plasma concentrations of FDA-approved manual intramuscular and subcutaneous injections of epinephrine.

Patients with a history of allergic rhinitis were randomly assigned to receive a single dose of epinephrine by means of manual intramuscular (0.3 mg, 21-gauge $\times$ 1" needle) (IM) or a manual subcutaneous (0.3 mg, 25-gauge $\times$ 5/8" needle) (SC) injection in a crossover manner. Per the epinephrine label, all injections were administered into the anterolateral aspect of the thigh by trained medical personnel. Blood samples for pharmacokinetic analyses were collected at pre-dose (at -10 and -5 min) and at 2, 4, 6, 8, 10, 12.5, 15, 20, 30, 45, 60, 90, 120, 150, 180, 240, 360, and 480 minutes after dosing. Because the reversal of a severe allergic reaction is expected to be achieved within 5 to 15 minutes of epinephrine administration, assessment within 15 minutes was included in the analysis. Pharmacokinetic plasma concentration-time data were analyzed using noncompartmental methods. Point estimates (least squares mean ratios) with 90% confidence intervals were calculated by natural log-transformed concentration data, and the statistical significance was evaluated. The study was approved by the Novum Independent Institutional Review Board, and all study participants provided written informed consent for participation.

A total of 36 patients (61% men; age, 19–55 years; mean $\pm$ SD weight, 76.5 ± 13.4 kg; mean $\pm$ SD body mass index, 25.5 ± 3.04 kg/m²) with a history of allergic rhinitis were enrolled and received IM and SC epinephrine injections. The mean plasma epinephrine concentration-time profiles for both 480 minutes and 15 minutes scales are presented in Figure 1. The mean maximum plasma concentration ($C_{\max}$) for the full 480 minutes was 270 pg/mL after IM injection and

246 pg/mL after SC injection ($P = .33$). The mean $C_{\max}$ for the first 15 minutes was 137 pg/mL after IM injection and 107 pg/mL after SC injection ($P = .70$). The median time to maximum plasma concentration ($T_{\max}$) for the full 480 minutes was 45 minutes for both treatments and the median $T_{\max}$ for the first 15 minutes was 8 minutes after IM injection and 10 minutes after SC injection. For the first 8 minutes, the partial area under the curves (AUCs) after IM injection was higher than after SC injection ($P = .003$ to $.03$). Overall exposure, as measured by the total AUC and the partial AUCs at 0 to 360 minutes was higher after SC injection ($P = .04$ and $P = .02$, respectively).

The results revealed that IM injection results in more rapid absorption during the first 8 minutes after injection, but SC injection results in higher overall epinephrine exposure throughout the entire sampling period. These differences seem to be minimal relative to the differences between manual IM injection and an epinephrine autoinjector (EpiPen, Meridian Medical Technologies, Columbia, Maryland); the mean $C_{\max}$ after EpiPen injection to the midanterolateral thigh ranged from 500 to 530 pg/mL with a median $T_{\max}$ of 9 to 30 minutes, whereas $C_{\max}$ after manual IM injection ranged from 310 to 400 pg/mL with a median $T_{\max}$ of 40 to 50 minutes.³ These relatively comparable pharmacokinetics between IM and SC injections may support the acceptance that manual IM and SC injections were considered equally efficacious before the report that the pharmacokinetics after IM injection in the thigh was superior to SC injection that was injected into the arm.^{5–7} Of note, the FDA has continued to maintain labeling including the SC route for epinephrine injection products with the same instructions as IM injection over the years.

In this report, we analyzed the pharmacokinetics of epinephrine during the first 15 minutes postdose to explore the concentration that will initiate a reversal of symptoms. The first 15 minutes postdose was chosen because guidelines (on the basis of extensive clinical experience) found that reversal of symptoms is typically achieved within 5 to 15 minutes postdose, an observation that is consistent with epinephrine labeling. The mean epinephrine concentrations at 5 and 15 minutes after dosing ranged from 70 to 100 pg/mL after IM injection and 50 to 90 pg/mL after SC injection. Given that initial symptoms alleviated include the symptoms of respiratory difficulty, swelling, or rash,⁸ it is reasonable to assume that the high-affinity β_2 receptors are activated at these concentrations.

However, it is important to note that absorption of epinephrine may be altered during acute allergic reactions because of the alternation of blood supply to muscle and subcutaneous tissue.¹ During anaphylaxis, the venous return may be reduced because of tissue extravasation and vasodilatation.⁹ Thus, epinephrine administered in the thigh may not enter systemic circulation as efficiently during

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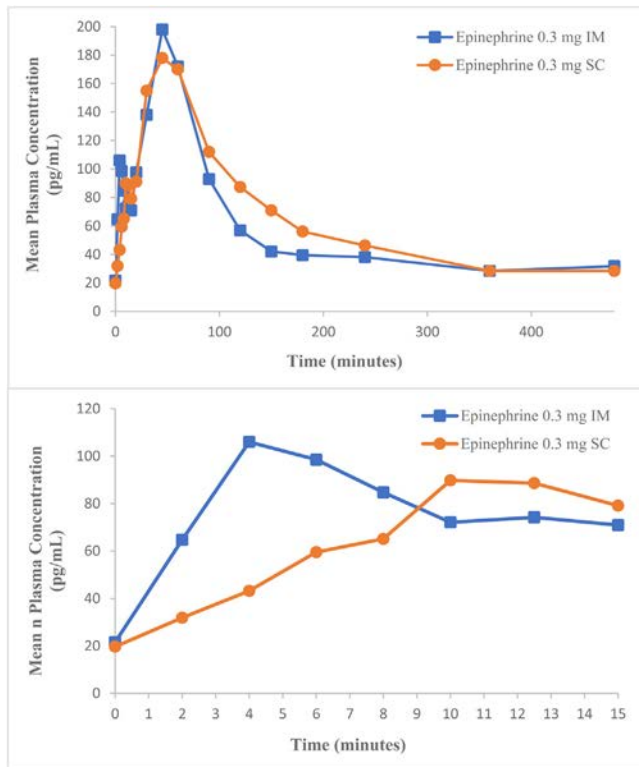


Figure 1. Mean plasma epinephrine concentration vs time after epinephrine 0.3 mg manual intramuscular and epinephrine 0.3 mg manual subcutaneous injections (480 minutes and 15 minutes scales). IM, intramuscular injection; SC, subcutaneous injection.

anaphylaxis. If that is the case, the levels of epinephrine should not exceed what is seen in healthy volunteers in which venous return is maintained.

In conclusion, the results of this Good Clinical Practice-compliant study revealed that there were minimal differences in overall pharmacokinetics between manual IM and SC administration of epinephrine. This finding is consistent with the current FDA labeling and with past guidelines in which IM and SC administration were considered

equally efficacious for the treatment of severe allergic reactions and anaphylaxis.

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References

- Turner PJ, Muraro A, Roberts G. Pharmacokinetics of adrenaline autoinjectors. *Clin Exp Allergy*. 2022;52(1):18–28.
- Duvauchelle T, Robert P, Donazzolo Y, Loyau S, Orlandini B, Leher P, et al. Bioavailability and cardiovascular effects of adrenaline administered by anapen autoinjector in healthy volunteers. *J Allergy Clin Immunol Pract*. 2018;6(4):1257–1263.
- Worm M, Nguyen D, Rackley R, Muraro A, Du Toit G, Lawrence T, et al. Epinephrine delivery via EpiPen[®] Auto-Injector or manual syringe across participants with a wide range of skin-to-muscle distances. *Clin Transl Allergy*. 2020;10:21.
- Muraro A, Worm M, Alviani C, Cardona V, DunnGalvin A, Garvey LH, et al. EAACI guidelines: Anaphylaxis (2021 update). *Allergy*. 2022;77(2):357–377.
- Simons FE, Gu X, Simons KJ. Epinephrine absorption in adults: intramuscular versus subcutaneous injection. *J Allergy Clin Immunol*. 2001;108(5):871–873.
- Fisher M. Treating anaphylaxis with sympathomimetic drugs. *BMJ*. 1992;305(6862):1107–1108.
- Ellis AK, Day JH. The role of epinephrine in the treatment of anaphylaxis. *Curr Allergy Asthma Rep*. 2003;3(1):11–14.
- Lindbeck GH, Burns DM, Rockwell DD. Out-of-hospital provider use of epinephrine for allergic reactions: pilot program. *Acad Emerg Med*. 1995;2(7):592–596.
- Dodd A, Hughes A, Turner PJ. Anaphylaxis management - Why are guidelines inconsistent? A rapid review of advanced life support guidelines for cardiac arrest associated with anaphylaxis. *Resuscitation*. 2021;159:165–167.

Going on vacation increases risk of severe accidental allergic reaction in children and adolescents



Short holiday breaks with family, away from routine and familiar surroundings, are an important part of childhood.¹ To date, studies of the risks for people with allergy, while on holiday, evaluate accidental allergic reactions (AARs) aboard airplanes or avoidance strategies of adults with nut allergy.^{2–4} There are limited published data on the risk of vacation-related accidental allergic reactions (VAARs) in children with food allergy (FA), who most often have multiple allergies.⁵

Their use of restaurants vs self-catering has not been defined. We report VAARs in children with FA who routinely attend an Irish tertiary allergy clinic.

A prospective observational study “ReAACT” (Recording Accidental Allergic Reactions in Children and Teenagers) recruited children aged 2 to 16 years with confirmed FA from Children's Health Ireland (CHI). Participants prospectively reported AARs by phone at 3-month intervals for 1 year. Vacation or holiday was defined as overnight stays away from home for recreational purposes. Participants were

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