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Intramuscular versus subcutaneous injection of epinephrine in the treatment of anaphylaxis

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To the Editor:

Epinephrine injection is the standard initial treatment for anaphylaxis. The ideal route of epinephrine injection in anaphylaxis has not been well established in clinical trials, and perhaps this cannot be tested because of ethical considerations. Various position statements and expert opinions recommend both intramuscular (IM) and subcutaneous (SC) routes of injection.¹

The product label of EpiPen, the only autoinjection epinephrine product approved in the US for anaphylaxis, recommends IM intramuscular injection into the anterolateral aspect of the thigh, but it also states that epinephrine, when given intramuscularly or subcutaneously, has a rapid onset of action, which supports both the IM and SC routes.² Whether there is any clinical difference between IM epinephrine injection and SC epinephrine injection is not known, and this needs to be studied.

Recently, this Journal published results of a pharmacokinetic study, conducted in adult males, that compared the systemic absorption of epinephrine injected either intramuscularly or subcutaneously in the deltoid area of the arm and injected intramuscularly in the vastus lateralis area of the thigh.³ This was an important study that warrants further comments and

discussion.

The authors' conclusion that IM injection of epinephrine into the thigh in adults is superior to injection into other sites is an intuitive sensible conclusion. However, the data do not establish that IM injection is superior to SC injection in the thigh. The mean plasma concentration of epinephrine was higher after SC injection than after IM injection in the deltoid area (2877 pg/mL after SC injection; 1821 pg/mL after IM injection). This suggests that in some sites the absorption after SC injection might be superior to the absorption after IM injection. Comparative data for IM injection and SC injection in the thigh in adults are not available, and the authors did not inject epinephrine SC into the thigh in this study. Such comparative data would be useful, because the EpiPen product label states that patients should inject epinephrine only into the anterolateral aspect of the thigh. If IM injection and SC injection in the thigh were similar with respect to relative systemic absorption of epinephrine—which is possible, according to IM and SC absorption data from the arm—that would go against authors' recommendation that IM is the preferred route of epinephrine injection.

In an actual clinical setting, an EpiPen injection might end up being either IM or SC, depending on various factors, such as the patient's sex, the body habitus, the amount of clothing through which the needle has to travel, etc. The length of the EpiPen needle is 14.29 mm. In an imaging study in diabetic adult patients (mean age, 40 years; mean body mass index, 24.6 kg/m²), the subcutaneous tissue layer was thicker in women than in men at all standard sites for insulin injection. For example, the mean subcutaneous tissue depth for the lateral thigh in women was 16.4 mm; this compared with 6.3 mm in men.⁴ The length of the EpiPen needle is therefore not large enough to ensure IM injection in many women and in some men. In the study published in this Journal,³ the mean BMI of study subjects was fairly high (mean, 36.6; range, 20-64), and some subjects' BMIs were in the obese range. It is possible that in some subjects the EpiPen injections were SC, not (as was assumed in the article) IM. Stratifying the data on the basis of BMI or, even better, on the basis of the actual thickness of the subcutaneous tissue of the thigh, would be informative. There are no reports to suggest that patients who are more likely to get autoinjected epinephrine SC, such as females and patients with large body habitus, have worse outcomes during anaphylaxis. However, the absence of reports does not establish that such a difference might not exist, and it would be an important public health issue if such a difference did exist. Therefore, additional studies should be done to address the important question of whether the route of epinephrine injection into the anterolateral thigh—IM or SC—makes a difference in terms of plasma concentration or in terms of clinical outcome. The study reported in the JACI³ and another, similar study conducted in children by the same authors are important milestones in this direction.

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Badrul Alam Chowdhury, MD, PhD

Robert James Meyer, MD
Division of Pulmonary and Allergy Drug Products
Center for Drug Evaluation and Research
US Food and Drug Administration

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ABSTRACT

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