

Clinical Communications

Anatomic and anthropometric determinants of intramuscular versus subcutaneous administration in children with epinephrine autoinjectors

Daniel C. Bewick, MD^a, Neville B. Wright, MD^b,
Richard S. Pumphrey, MD^a, and
Peter D. Arkwright, MD, DPhil^a

Clinical Implications

- Intramuscular rather than subcutaneous delivery of epinephrine is important for optimal treatment of anaphylaxis.
- To achieve this in children, the autoinjector should be positioned at least half way down the outer thigh, which is particularly important for patients who are obese.

TO THE EDITOR:

Intramuscular epinephrine is the first-line treatment for patients with anaphylaxis. The 2012 World Allergy Organization anaphylaxis guidelines recommend the mid-anterolateral thigh as the preferred site of injection.¹ The deltoid muscle and the subcutaneous route are not recommended because studies in adults have shown that mean plasma epinephrine concentration is significantly lower and that peak concentration may not be reached for more than 1 hour after injection.² In a study of 17 children, subcutaneous injection led to only 2 of 9 (22%) achieving maximal epinephrine concentration within 5 minutes, compared with 6 of 8 (75%) if the injection was intramuscular.³

With increasing obesity in both adults and children there are growing concerns that autoinjectors will not deliver epinephrine into the muscle in a significant proportion of patients. A study of American adults showed that 1 of 50 men and 21 of 50 women, many with high body mass indices (BMI), had skin surface-to-muscle thickness greater than the autoinjector needle length.⁴ In another study, of 256 American children, 19% of children who weighed <30 kg and 30% of children who weighed >30 kg also had skin-to-muscle depth greater than the needle length.⁵ The EpiPen (Dey, Napa, Calif) is currently the most common autoinjector used in the United States and the United Kingdom, and the needle length for the 0.15-mg device recommended for children <30 kg is 12.7 mm, and the 0.30 mg device for heavier children has a needle length of 15.9 mm. Other epinephrine autoinjectors available for use in children, including Auvi-Q (Sanofi US, Bridgewater, NJ) and Adrenaclick (Amedra Pharmaceuticals LLC, Horsham, Pa) in the United States and JEXT (ALK-Abelló Ltd, Reading, Berkshire, UK) in the United Kingdom, have the same needle lengths.

In this prospective study, we recruited 93 children (age range, 1-16 years) with food allergies who attended our regional pediatric allergy outpatient clinics over a 6-month period in mid-2012. The study was approved by the research ethics committee, and written consent was obtained from all the participants. Fifty-nine children were white (63%) and 25 were Asian (27%). Using a MicroMaxx portable ultrasound machine with a linear

HFL38/13.6 MHz probe (SonoSite Inc, Bothell, Wash), we measured the distance from the skin surface to the vastus lateralis muscle interface at 3 distances along the outer thigh (one-fourth [proximal thigh], one-half [mid-thigh], and three-fourths [distal thigh] the distance from the greater trochanter to the lateral epicondyle of the femur) as determined with a tape measure. The skin surface-to-gastrocnemius muscle depth midway between the tibial tuberosity and the lateral malleolus of the ankle (mid-calf) also was measured. The mean of triplicate measurements is quoted. All measurements were made by 1 observer (D.C.B.) trained in the use of the ultrasound machine by a consultant pediatric radiologist. Weight, height, and waist circumference were also measured, and BMI as well as age- and sex-appropriate BMI centiles were calculated.

The age, sex, and anthropometric characteristics of children are summarized in Table I. Particularly in children >30 kg, skin surface-to-muscle depth increased significantly the more proximally up the thigh the measurements were made. The median skin surface-to-muscle depth was 5.6 mm (interquartile range, 1.5-9.3 mm) greater at the proximal thigh than at the mid-thigh. Sixty one percent children weighing >30 kg had a proximal thigh skin surface-to-muscle depth that was greater than the autoinjector needle length compared with only 13% at the distal thigh. Measurements of obesity, including weight ($P = .004$), BMI ($P < .001$), and waist circumference ($P < .001$), but not age or sex, were predictive of children whose skin surface-to-muscle depth was greater than the autoinjector needle length (multivariate analysis).

By using US National Center for Health Statistics children's BMI growth charts (www.cdc.gov/growthcharts), 10% of children in the cohort were overweight (85th to 94th centile for age) and 18% were obese (>95th centile for age). There were no significant differences in obesity in white and Asian children. At the proximal thigh, 82% of the children who were obese, but only 25% of children of a healthy weight, had skin surface-to-muscle depth greater than the needle length. At the distal thigh, 17% of children who were obese and 2% of children of a healthy weight had a skin-to-muscle depth greater than the needle length (Figure 1).

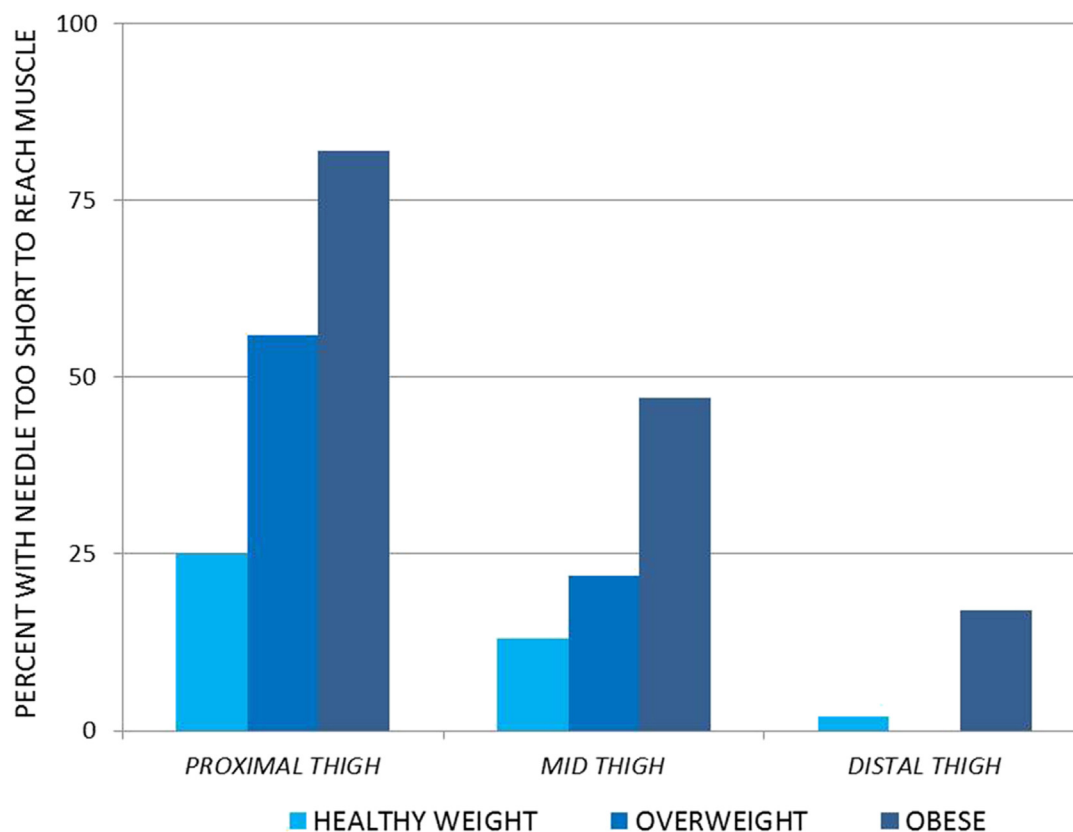
Compression of tissues during firing of autoinjectors might be expected to reduce skin surface-to-muscle depth and, therefore, increase the chance of intramuscular injection.⁶ To examine this possibility, skin surface-to-muscle depth was measured in a subgroup of 7 children ages 5 to 14 years (median, 8 years), after applying enough pressure with a trainer EpiPen and an adjacently placed ultrasound probe positioned on the outer mid-thigh to trigger the device. The EpiPen trainer is a reasonable surrogate for the medicinal device because it has previously been shown to require equivalent force for activation.⁷ The median compression was 0.5 mm (interquartile range, 0.0-1.2 mm). In 3 children younger than 7 years old there was little or no change in skin surface-to-muscle depth after compression. In the overall cohort, the skin-to-muscle depth at the mid-thigh was 2.4 mm (0.8-3.2 mm) greater than the needle length, which suggests that compression of tissues when firing autoinjectors would not alter the proportion of children whose injection was subcutaneous rather than intramuscular. There was no significant correlation between BMI or age and change in depth with compression.

TABLE I. Anthropometric measures of 93 children referred to the local pediatric allergy service

Parameter*	Children <30 kg weight	Children ≥30 kg weight	All children
No. (%)	62 (67)	31 (33)	93 (100)
Age (y), median (IQR)	4 (2-6)	12 (8-14)	6 (3-10)
Boys, no. (%)	35 (57)	19 (61)	54 (58)
Weight (kg), median (IQR)	16.6 (12.2-20.8)	43.8 (38.4-53.3)	20.8 (14.5-38.6)
Height (cm), median (IQR)	102 (88-114)	150 (140-159)	114 (96-141)
BMI (kg/m ²), median (IQR)	16.1 (15.5-17.1)	19.9 (18.2-22.4)	16.8 (15.7-19.1)
Waist circumference (cm), median (IQR)	52 (49-56)	75 (68-80)	56 (51-68)
Skin surface-to-muscle depth (mm), median (IQR)			
Proximal thigh	10.0 (8.3-13.2)	19.2 (12.8-25.7)	12.0 (8.6-16.9)
Mid-thigh	8.4 (7.0-10.2)	12.2 (7.8-16.5)	8.8 (7.0-12.9)
Distal thigh	6.8 (5.8-8.5)	9.7 (7.2-12.2)	7.9 (5.9-9.6)
Mid-calf	7.0 (6.2-7.2)	9.5 (8.6-10.5)	8.5 (7.0-9.8)
Skin surface-to-muscle depth greater than needle length (mm)	>12.7	>15.9	
Proximal thigh, no. (%)	17 (27)	19 (61)	36 (39)
Mid-thigh, no. (%)	10 (16)	9 (29)	19 (0)
Distal thigh, no. (%)	1 (2)	4 (13)	5 (5)
Mid-calf, no. (%)	0 (0)	0 (0)	0 (0)

IQR, Interquartile range.

*The median (IQR) is based on triplicate measurements.

**FIGURE 1.** Percentage of children whose skin surface-to-muscle depth was greater than the autoinjector needle length based level of obesity defined by age-corrected BMI (www.cdc.gov/obesity/childhood/basics.html). Healthy weight (BMI <85th percentile) n = 67 (72%), overweight (BMI 85th-94th percentile) n = 9 (10%), obese (BMI ≥95th percentile) n = 17 (18%). Differences within all groups were statistically significant, with a $P < .001$ (χ^2 test).

A possible concern of injections into the distal thigh is the risk of the needle going into the bone. Skin surface-to-bone depth, therefore, was measured at the distal thigh in 11 children ages 1 to 15 years, with BMI units (kg/m^2) that ranged from 14 to 27 (median, 17). The median depth was 29.5 mm (interquartile range, 21–36 mm). The thinnest skin-to-bone depth was 16.2 mm in a 5-year-old child with a BMI of only 14 and a weight of 15 kg, who, in an emergency, would have used an autoinjector with the 12-mm needle.

This study provides novel and important information regarding the appropriate placement of epinephrine autoinjectors for intramuscular rather than subcutaneous injection. Although skin-to-muscle depth may be reduced in the process of triggering the device, in most children, it will not be sufficient to reduce the thickness to less than the needle length. A new epinephrine autoinjector, Emerade (Medeca Pharma AB, Uppsala, Sweden) with longer needle lengths (16 mm for children <30 kg and 25 mm for children and adults over this weight), currently scheduled for launch in the United Kingdom and other northern European countries at the end of 2013, will improve the chance of intramuscular injection in patients who are obese. Particularly in children who are obese, it is important to ensure that the epinephrine is injected at least half way down the thigh. Injection lower down the thigh or even into the mid-calf might be considered if there is no response to the first dose given into the thigh. Similar studies should be performed in adults as well as in children in other parts of the world to determine how universal these findings are.

^aDepartment of Pediatric Allergy and Immunology, Royal Manchester Children's Hospital, University of Manchester, United Kingdom

^bDepartment of Pediatric Radiology, Royal Manchester Children's Hospital, University of Manchester, United Kingdom

No funding was received for this work.

Conflicts of interest: P. D. Arkwright has received travel support from Meda Pharmaceuticals. R. S. Pumphrey has consultant arrangements with Meda Pharmaceutical; has provided expert testimony for Her Majesty's Coroner; has received payment for lectures from Quasafe; and has received travel support from Lincoln Medical. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication April 15, 2013; revised August 1, 2013; accepted for publication August 8, 2013.

Available online ■ ■

Cite this article as: Bewick DC, Wright NB, Pumphrey RS, Arkwright PD. Anatomic and anthropometric determinants of intramuscular versus subcutaneous administration in children with epinephrine autoinjectors. *J Allergy Clin Immunol Pract*. <http://dx.doi.org/10.1016/j.jaip.2013.08.004>.

Corresponding author: Peter D. Arkwright, MD, DPhil, University of Manchester, Royal Manchester Children's Hospital, Manchester, M13 9WL, United Kingdom. E-mail: peter.arkwright@nhs.net.

2213-2198/\$36.00

© 2013 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaip.2013.08.004>

REFERENCES

1. Simons FE, Arduzzo LR, Bilò MB, Dimov V, Ebisawa M, El-Gamal YM, et al. 2012 update: World Allergy Organization Guidelines for the assessment and management of anaphylaxis. *Curr Opin Allergy Clin Immunol* 2012;12:389-99.
2. Simons FE, Gu X, Simons KJ. Epinephrine absorption in adults: intramuscular versus subcutaneous injection. *J Allergy Clin Immunol* 2001;108:871-3.
3. Simons FE, Roberts JR, Gu X, Simons KJ. Epinephrine absorption in children with a history of anaphylaxis. *J Allergy Clin Immunol* 1998;101:33-7.
4. Song TT, Nelson MR, Chang JH, Engler RJ, Chowdhury BA. Adequacy of the epinephrine autoinjector needle length in delivering epinephrine to the intramuscular tissues. *Ann Allergy Asthma Immunol* 2005;94:539-42.
5. Stecher D, Bulloch B, Sales J, Schaefer C, Keahey L. Epinephrine auto-injectors: is needle length adequate for delivery of epinephrine intramuscularly? *Pediatrics* 2009;124:65-70.
6. Schwartz A, Seeger H. Are adrenaline autoinjectors fit for purpose? A pilot study of the mechanism and injection performance characteristics of a cartridge-versus a syringe-based autoinjector. *J Asthma Allergy* 2010;3:159-67.
7. Jacobsen RC, Guess TM, Burks AW. Comparing activation and recoil forces generated by epinephrine autoinjector and their training devices. *J Allergy Clin Immunol* 2012;129:1143-5.e4.