Epinephrine Auto-Injector Needle Length (Does Height or BMI add Valuable Information in Adults?)

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Abstract: Background: Some overweight and obese adults have an increased risk of subcutaneous injection using epinephrine auto injectors (EAI). Needle lengths of EAI vary between brands and lots. Objective: To study if BMI or height adds information to define adults at risk of having intraosseous or subcutaneous injection. Methods: Ninety-nine (99) food allergic adult patients, 32 men and 67 women, 18 – 72 years of age, prescribed EAI were included. The skin to muscle and skin to bone distances were measured by ultrasonography. The effect of injection on naked skin or through thick clothing was analyzed. High and minimal pressure was applied to the ultrasound probe. Results: Among three men and 1/5 women with BMI <20 had a risk of intraosseous/intraosseous injection using the high pressure auto injector Epipen®, thick clothing, 5/8. Injecting through naked skin using the shortest needle, 14/17 obese women had a high risk of subcutaneous injection (overweight 14/23), through thick clothing all 17 obese women would have a risk of subcutaneous injection (overweight 20/23). Injecting with LPEAI through naked skin, using the shortest needle 8/17 obese and 4/23 overweight women would have a risk of subcutaneous injection, wearing thick clothing, 10/17 obese and 7/23 overweight women. Height did not predict a value. Conclusion: Using high pressure EAI, high BMI predicted a high risk for subcutaneous injection in women and in some men. Even injection with low pressure EAI had some risk of subcutaneous injection, especially when injected through thick clothing. Height did not have predictive value.

Keywords: Auto-injector; epinephrine; intramuscular; subcutaneous; intraosseous; skin to bone distance; skin to muscle distance; clothing; overweight; obese; adults; women; men.

Abbreviation: (AI = Auto-injector) (EAI = Epinephrine Auto-injector) (HPEAI = High Pressure EAI) (LPEAI = Low Pressure EAI) (STMD = Skin to muscle distance) (STBD = Skin to bone distance) (STMDmax = Skin to muscle distance, high pressure, 8 lb ≈ 35 N) (STBDmax = Skin to bone distance, high pressure) (STBDmax = Skin to bone distance, low pressure) (STBDmax = Skin to bone distance, high pressure, 8 lb ≈ 35 N) (SC = Subcutaneous) (IM = Intramuscular) (i.o./p. = Intraosseous/periosteal)

INTRODUCTION

In a previous paper, Tsai et al. (1) described a cohort of 99 adults with food allergy. Later, we have described the relation between the skin to muscle distance (STMD) and skin to bone distance (STBD) and weight (2-7). Some, but not all overweight adults, adolescents and children as well as obese women had a STMD indicating a risk of subcutaneous (SC) injection. In emergency rooms, intramuscular (IM) injection of epinephrine is often given using one inch needles (25 mm). Since 1980, epinephrine autoinjectors (EAI) have been used for treatment of generalized allergic reactions/anaphylaxis in the community. These devices are either high pressure EAI (HPEAI) or low pressure EAI (LPEAI). There are several HPEAI on the market (Epipen®, Auvi-Q®, Emerade® etc.), only one low pressure LPEAI, Emerade®. Generally, HPEAI have shorter exposed needles (mean needle length 8-16 mm) than LPEAI (16-23 mm) (Table 1). Furthermore, the precision of the production of the needles varies between manufacturers. The range of exposed needle lengths accepted for batch release varies and is five (5) mm for Epipen®, 2.6 mm for Auvi-Q®/Emerade® 0.1 mg, 1.7 mm for Emerade® 0.15 mg and 1.5 mm for Emerade® 0.3 mg and 0.5 mg (4). The prescribing physicians and their patients do not know the true length of the needle of the actual device prescribed to the patient. Therefore, the worst case scenario must be considered when calculating risks of IM or SC injections. We should consider the longest needle that is accepted by the manufacturer for batch release for estimation of the risk of intraosseous/intraosseous injection and the shortest needle for estimation of the risk for SC injection. We must also consider the shortest allowable needle length when injected through thick clothing.

At the time of the original studies (1, 9, 10), we did not know the variation in pressure on the device, to release the needle, accepted for batch release. Later, the manufacturers of three brands (Epipen®, Auvi-Q® and Emerade®) have kindly supplied us with their specifications on the pressures accepted for batch release (11). This information could not be included in the present analysis. Therefore, in this study, the high and low pressure terms refer to the pressure used by Kim et al. in the original studies (1, 9, 10), i.e. for “high pressure” about 8 lb or 35 Newtons (N) and “low pressure” as minimal pressure on the probe. Even Worms et al. (12) use the same vocabulary in their recent study.

In this paper, we will assess whether patients’ BMI or height would improve the ability to identify adults who are at risk of SC or i.o./p. injection using the variation in needle length as reported by three EAI presently available in North America and/or Europe (4) and the pressures used in the original studies by Kim et al. (1, 9, 10).
| EAI               | Lower and upper limits for needle length | STMD – orifice 2 mm | STMD – orifice 2 mm – thick clothes 3 mm | STBD Naked skin Full length mm | STBD thick clothes mm | Variation of needle length mm |
|------------------|-----------------------------------------|---------------------|------------------------------------------|-------------------------------|-----------------------|-----------------------------|
| HPEAI – high pressure EAI |                                         |                     |                                          |                               |                       |                             |
| Epipen Jr® 0.15 mg | Lower Limit                             | 8                   | 5                                        | 10                            | 7                     |                               |
|                   | Upper Limit                             | 13                  | 10                                       | 15                            | 12                    |                               |
| Epipen® 0.3 mg    | Lower Limit                             | 11                  | 18                                       | 8                             | 15                    | 11                           |
|                   | Upper Limit                             | 16                  | 23                                       | 13                            | 20                    | 16                           |
| Auvi-Q® 0.1mm     | Lower Limit                             | 4.4                 | 1.4                                      | 6.4                           | 3.4                   |                               |
|                   | Upper Limit                             | 6.9                 | 3.9                                      | 8.9                           | 5.9                   |                               |
| Auvi-Q® 0.15 mg   | Lower Limit                             | 9.4                 | 6.4                                      | 11.4                          | 8.4                   |                               |
|                   | Upper Limit                             | 12                  | 9                                        | 14                            | 11                    |                               |
| Auvi-Q® 0.3 mg    | Lower Limit                             | 12.7                | 9.7                                      | 14.7                          | 11.7                  |                               |
|                   | Upper Limit                             | 15.3                | 12.3                                     | 17.3                          | 15.3                  |                               |
| LPEAI – low pressure EAI |                                      |                     |                                          |                               |                       |                             |
| Emerade® 0.15 mg  | Lower Limit                             | 13                  | 10.0                                     | 15                            | 12                    |                               |
|                   | Upper Limit                             | 14.7                | 117                                      | 16.7                          | 13.7                  |                               |
| Emerade® 0.3 mg   | Lower Limit                             | 20.1                | 32.5                                     | 17.1                          | 29.5                  | 22.1                         |
|                   | Upper Limit                             | 21.6                | 34.0                                     | 18.6                          | 31.0                  | 23.6                         |
| Emerade® 0.5 mg   | Lower Limit                             | 20.1                | 32.5                                     | 17.1                          | 29.5                  | 22.1                         |
|                   | Upper Limit                             | 21.6                | 34.0                                     | 18.6                          | 31.0                  | 23.6                         |

Table 1: The needle lengths of three EAI s available in North America and Europe in 2019. Needle lengths are given according to the manufacturers’ approved specifications (4). The STMD is based on Diacono et al. (7) by subtracting 2 mm from the penetrating needle length, i.e. 2 mm for the eye of the needle. The STBD is based on the full length of the needle. Both STMD and STBD are given for the case injection is performed on naked skin and with winter clothes. The thickness of compressed winter clothes, 3 mm is an example. However, the thickness of winter clothes varies. The possible length of longer EAI needles is indicated as possible in Figure 5.

| EAI brand | Activation for, Newtons (N) | Pressure on the probe in this study (N) |
|-----------|-----------------------------|----------------------------------------|
|           | Range                       | Mean                                   |                                         |
| HPEAI     |                             |                                        |                                         |
| Epipen®   | 8.5 - 35                    | 21                                     | About 35                                |
| Auvi-Q®   | 8.5 - 53                    | 27                                     | About 35                                |
| LPEAI     |                             |                                        |                                         |
| Emerade®  | 8 - 25                      | 16                                     | Minimal                                 |

Table 2: Activation pressure in Newtons (N) as supplied by the manufacturers. Modified after (11).
METHODS

Ninety-nine adults (18-72 yrs), 67 women, and 32 men were included (1). Seventeen of the 67 women (25%) were obese (BMI ≥30 kg/m²) and 23/67 (34%) overweight (BMI ≥25-<30 kg/ m²). Among the men, 22/32 (69%) were obese (8/32) or overweight (12/32) (1).

Basic statistics have been published in the original paper (1) and different aspects on EAI needle length has been included in a series of papers (2-4, 6, 7, 9-11), including children, adolescents and adults.

The 99 adult food allergic patients included in this study gave their written, informed consent before participating in the original study (1).

We determined the skin to bone distance, STBD, and the skin to muscle distance, STMD by ultrasound. High pressure (>8 lb = 35 N) and minimal pressure was applied to the ultrasound probe pressed against the mid third of the anterior-lateral aspect of the right thigh. At the time of establishing the protocol of the study, the pressure to be applied for each EAI (mean and range of pressure accepted for batch release) was not known to us and has subsequently been published (11), Table 2.

The STMD was measured from the skin surface to the outer surface of the facia lata. As in our previous studies we used the data by Diacono et al. (13) who found the whole needle orifice must pass completely into the muscle for proper administration of an IM injection. The finding by Diacono et al. was supported by Duvauchelle et al. (14), who published a figure (Figure 2 in (14)) showing the epinephrine bolus staying at the tip of the injection needle in the SC tissue. Ten (10/12) obese women who received injections with an EAI with short needle, Anapen®, received a subcutaneous (SC) injection, as verified by ultrasound (14). Song has proposed that the jet from the EAI needles would push the epinephrine bolus through the fascia (13). The data by Diacono et al. (13) and Duvauchelle et al. (14) confirm that the jet from the injection would not likely penetrate through the fascia. The length of the needle eye of the EAI needles were estimated to be 2 mm (2). Therefore, the needle length was reduced by 2 mm when estimating the risk for SC injection (6).

Using calipers, the thickness of three men’s winter clothing found to be about 3 mm thick. Therefore, we used 3 mm as an estimate of winter clothing thickness and the needle length was reduced by 3 mm when estimating the risks for i.o./p or SC injecting through wearing thick clothes totally 5 mm when calculating the distance to the muscle. We note that people may have thinner or thicker winter clothes, e.g. 2 or 5 mm. The impact of other thicknesses of clothes can be calculated applying data in the figures. The needle lengths used for calculation of the risk of i.o./p and SC injection are given in Table 1 (6).

The calculated data is presented for each specific brand of EAI since the accepted variation in needle length differed between brands, for the HPEAI, Epipen® (5 mm), for Auvi-Q® (2.6 mm) (Figures 1, 3 and 5) and for the LPEAI, Emerade® for the shorter needle 0.15 mg dose (1.7 mm) for the longer needle 0.3 and 0.5 mg epinephrine (1.5 mm) (Figures 2, 4 and 5).

STATISTICS

The risk of SC or i.o./p, injection is illustrated by plotting the STMD or STBD, respectively on the Y-axis and weight on the X-axis with BMI kg/m² classes or height classes marked in the scattergrams, Figures 1-4. In addition, we plotted the STBD max and STMD max to the left and STBD min and STMD min to the right versus BMI, Figure 5. This was to compare the properties of HPEAIs with LPEAIs using BMI as predictor. The numbers of BMI and height categories were calculated in Excel, using appropriate formulas.

For statistical analyses, Statistica, version 13.0.159.0, was used (Students t-test and ManWitney U-test), Statistica, 13.0.159.0, was also used for construction of the figures. Student t-test was used to calculate possible differences between men and women, Table 3. The ManWitney U-test was used to test differences between STBD max, STBD min, STMD max and STMD min.

The figures are intended to give an idea about the suitability of the EAI’s to be used for treatment of general allergic reactions in the community. Since distances are relatively small, the precision not absolute and the pressure not in accordance with manufacturers specifications, we used a semiquantitative color-based grading system to give an impression of major differences. White color indicates very low risk, 0-2 %, green color indicates low risk, 3-9 %, orange color indicates medium risk, 10-19%, and red color indicates high risk, >20 %, for injection into the bone (STBD) or the SC space (STMD)(4). Percentages ≥50 % are in bold in Table 5 A-D.

RESULTS

The patient characteristic data on age, height, weight, BMI and measured ultrasound distances are presented in Table 3. There was no significant difference between men and women regarding age, height, weight, BMI, STBD max, STMD max, STMD min or STMD min. In men and women, there was a significant difference between STBD max vs STBD min (p=0.000001), STBD max vs STMD max (p=0.000001), and STBD min vs. STMD min (p<0.01). In women, the correlation between STMD max vs STMD min was significant (p=0.006). In men, however, there was no significance (p=0.42), Table 3.

Among the above mentioned parameters tested for correlation (Table 3), weight versus BMI had the highest correlation (r=0.94 in men; r=0.92 in women). however, all other tested correlations were significant except for weight versus height, Table 3.

Height had no relation to weight (Table 3, Figure 1 – 4) for risks of non-intramuscular injection. The effect of using the longest and shortest allowable needles of the HPEAI Epipen® and the LPEAI Emerade® injected through naked skin and thick clothing of men and women is illustrated in Table 4 and 5A to 5D and Figures 1-4. In Table 6, the mean, median maximum and minimum values of height, weight, BMI, STBD and STMD for the BMI groups are presented.
Figure 1: The two upper figures show the relation between $\text{STBD}_{\text{max}}$ and weight in 32 men with food allergy, using high pressure. Weight is the most common guiding estimate to decide on dose of epinephrine and type of EAI. To the left, BMI is illustrated as given in the figure, to the right classes of heights. The two lower figures show the relation between STMDmax and weight in the same group. The red and green solid lines indicate the variation in needle length for Epipen® (red lines) and Auvi-Q® (green lines), respectively, and the broken red and green lines the shortest needle length when injecting through thick clothing (3 mm as an example).

Table 4 shows the distribution of patients at risk for i.o./p. injection (STBD) or SC injection (STMD). It appears that there is a higher risk of HPEAIs causing SC injection using the presently available needles especially in women. There is a higher risk for SC injections when injecting through thick clothing. This also applies to LPEAIs, but to a lesser extent. In Table 5 A – D, the data on the risk of SC or i.o./p. injection is presented. Each table is subdivided in an 1-section with data using the variation in needle length of the presently available EAs. The 2-sections show the effect on the frequency of SC injection using longer needles that would have a low risk of i.o./p. injection.

**Men**

Eight of 32 men were obese and 12/32 were overweight, i.e. 20/32 men, had BMI >25 kg/height m2, Figure 1 and Table 5A. The $\text{STBD}_{\text{max}}$ indicates that only one man had a risk of i.o./p. injection (1/3 with BMI <20 kg/height m2), Figure 1, Table 5A.

When Epipen® was injected through naked skin, 2/8 obese men (Auvi-Q® 1/8) had a risk of SC injection and four of eight (4/8) when Epipen® was injected through thick clothing (Auvi-Q® 3/8) (Figure 1 and 2). Among overweight men, 3/12 had a risk of subcutaneous injection when Epipen® with the shortest needle possible was injected through thick clothing, Figure 1 and Table 5A. Using a HPEAI and a longer needle, 1 inch or 25.4 mm, would eliminate the risk of SC injection at the cost of one (1/12) overweight men with a risk of i.o./p. injection, figure 1 and Table 5A. Using a LPEAI that has longer needle than the HPEAI and a longer needle, 1 inch or 25.4 mm, would eliminate the risk of SC injection at the thickness of clothing (3 mm as an example).

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Autoinjector needle length in obese adults

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Table 3: Basic data describing the sample of 32 men and 67 women investigated (partly reported in Tsai et al. (1)).
1) Man Whitney U-test; 2) t-test

Women

Of the 67 women, 23 (34%) were overweight and 17 (25%) were obese (Table 5C, Figure 3 and 4).

Using Epipen® or Auvi-Q, one of five (1/5) women with BMI less than 20 kg/height m2 had a risk of i.o./p. injection (Figure 3, Table 5C). She had a BMI of 19.4 kg/m2, a weight of 54 kg and a height of 167.6 cm. The risk of SC injection on the other hand was 100% for the group using a shortest needle and injecting through thick clothing (Table 5C, Figure 3 and 4).

Fourteen of 17 (14/17) obese and 13/23 overweight women had a risk of SC injection using Epipen®, even when injected through naked skin. A majority of overweight (20/23) and all obese (17/17) women would have a risk of SC injection if Epipen® was injected through thick clothing (Auvi-Q® 19/23 and 15/17, respectively). Among women with BMI <20 kg/height m2, 1/5 had a risk for SC injection when injected through naked skin with an Epipen® as well as with Auvi-Q®, and all five (5/5) when injected through thick clothing with Epipen® (Auvi-Q® 2/5).

Five normal weight women (5/22), 20-25 kg/m2, had a risk of SC injection using Epipen® when injected through naked skin (Auvi-Q® 2/22), and through thick clothes 16/22 would have that risk (Auvi-Q® 14/22) (Figure 3, Table 5C). Women weighing more than 80 kg injected with Epipen® or Auvi-Q® (all were obese) were not at risk of i.o/p injection even with the longest proposed needle length, 25 mm, as demonstrated in figure 3 and 5, upper left panel. At the same time, only 14/17 obese and 14/23 overweight women had a risk of SC injection.
Low pressure EAs (0.3 and 0.5 mg ephedrine) have longer needles than the HPEAs (0.3 mg epinephrine), with mean exposed needle length of 23 mm versus 15.5 mm for HPEAs. Despite that, there was no risk for i.o./p. injection in women using LPEAs (Figure 4, Table 5D).

When injecting with a LPEAI through naked skin, 8/17 obese women and 4/23 overweight women would have a risk of SC injection using the shortest needle approved for batch release, and when using the shortest needle approved, injecting through thick clothing, 11/17 obese and 12/23 overweight women would have a risk of SC injection, Figure 4, Table 5D.

Women weighing more than 80 kg all were obese and, when injected with an LPEAI, would tolerate even longer needles, the longest proposed length, 36 mm, when using an LPEAI, without any risk of i.o./p. injection among obese and overweight women as demonstrated in figure 4 and 5, upper right panel, Table 5D. With the longest proposed needle, only 1/17 obese women would have a risk of SC injection.

Figure 2: The relation between STBDmin/STMDmin, using an LPEAI, and weight in 32 men with food allergy, using low pressure. The symbols as in Figure 1, the LPEAI needle length/penetration length and variation in length is indicated in blue. The variation in needle lengths that of the LPEAI Emerade®.

BMI:  
- >=30
- >25 - <30
- >20 - >25
- <20

BMI:  
- >=30
- >25 - <30
- >20 - >25
- <20

Height:  
- >=165 to <170
- >170 to <175
- >175 to <180
- >180 to <185
- >185 to <190
- >195 to <200

Height:  
- >=165 to <170
- >170 to <175
- >175 to <180
- >180 to <185
- >185 to <190
- >195 to <200

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Using HPEAIs in men and women, BMI >20 kg/m² indicates no risk for i.o./p. injection but does not discriminate regarding SC injection (Figure 1 and 3). With the present needle length and the pressure used, BMI does not seem to discriminate between those at risk or not at risk of SC injection (Figure 1 and 3).

Using LPEAIs in men and women, there was no risk of i.o./p. injection or SC injection in men in any BMI group. In women, a few overweight and many obese women had a risk of SC injection (Figure 2 and 4, Table 5B and 5D). However, BMI did not discriminate between those at risk and those not at risk (Figure 4 and Table 5D).

In Figure 5 is shown STBD_{max} and STB_{min} and STMD_{max} and STMD_{min} in relation to BMI, showing no discrimination between those with and without risk of SC injection.

As illustrated in Figures 1-4, right panel, height classes did not discriminate between those at risk and not at risk of i.o./p. injection and SC injection, respectively.
| STBD/STMD mm*) | Men, n = 32 | Women, n = 67 | Women, obese, n = 17 |
|----------------|-------------|---------------|----------------------|
|                | Naked skin % | Thick clothing % | Naked skin % | Thick clothing % | Naked skin % | Thick clothing % |
| HPEAI (Epipen\textsuperscript{®})* |             |               |             |               |             |               |
| STBD\textsubscript{max} 11.0 | 0 | 0 | 0 | 0 | 0 | 0 |
| STBD\textsubscript{max} 13.0 | 0 | 0 | 0 | 0 | 0 | 0 |
| STBD\textsubscript{max} 16.0 | 3 | 1 | 1 | 0 | 0 | 0 |
| STBD\textsubscript{max} 18.0 **) | 6 | 6 | 1 | 1 | 0 | 0 |
| STBD\textsubscript{max} 20 | 25 | 3 | 0 | 0 | 0 | 0 |
| STBD\textsubscript{max} 23 | 25 | 7 | 0 | 0 | 0 | 0 |
| STBD\textsubscript{max} 25 | 33 | 13 | 0 | 0 | 0 | 0 |
| STBD\textsubscript{min} 19.1 | 0 | 0 | 0 | 0 | 0 | 0 |
| STBD\textsubscript{min} 20.6 | 0 | 0 | 0 | 0 | 0 | 0 |
| STBD\textsubscript{min} 22.1 | 3 | 0 | 0 | 0 | 0 | 0 |
| STBD\textsubscript{min} 23.6 | 0 | 0 | 0 | 0 | 0 | 0 |
| STBD\textsubscript{min} 31.5 **) | 0 | 0 | 0 | 0 | 0 | 0 |
| STBD\textsubscript{min} 33.0 | 0 | 0 | 0 | 0 | 0 | 0 |
| STBD\textsubscript{min} 34.5 | 3 | 3 | 2 | 0 | 0 | 0 |
| STBD\textsubscript{min} 36.0 | 9 | 19 | 0 | 0 | 0 | 0 |
| STMD\textsubscript{min} 17.1 | 0 | 0 | 39 | 67 | 0 | 0 |
| STMD\textsubscript{min} 18.6 | 0 | 0 | 28 | 61 | 0 | 0 |
| STMD\textsubscript{min} 20.1 | 0 | 0 | 18 | 44 | 0 | 0 |
| STMD\textsubscript{min} 21.6 | 0 | 0 | 12 | 33 | 0 | 0 |
| STMD\textsubscript{min} 29.5 **) | 0 | 0 | 2 | 6 | 0 | 0 |
| STMD\textsubscript{min} 31.0 | 0 | 0 | 2 | 6 | 0 | 0 |
| STMD\textsubscript{min} 32.5 | 0 | 0 | 0 | 6 | 0 | 0 |
| STMD\textsubscript{min} 34.0 | 0 | 0 | 0 | 0 | 0 | 0 |

Table 4: The risk of not injecting into the muscle for the HPEAI Epipen\textsuperscript{®} and the LPEAI, Emerade\textsuperscript{®}. Since distances are short, pressure not well specified etc., we used a semi-quantitative color system to point on problems (Three ref xx xx). White color indicates very low risk, 0-2%, green color indicates low risk, 3-9%, orange color indicates medium risk, 10-19%, red color high risk, i.e. higher risk than 20%, for injection into the bone or subcutaneous tissue, respectively. In this table, we added bold types to indicate a risk more than 50%. The exposed needle lengths are given in mm. White areas in column one indicate presently available needle lengths, yellow marked needle lengths in column one indicate possible longer needles for use in obese patients (>80 kg). For needle lengths, see Table 1. For more detailed analyses in thin (BMI <20 kg/m2), obese and overweight men and women, see Table 5 Aa to 5Db.

*) Present and possible needle length.

**) Possible suitable needle length in obese patients.
Autoinjector needle length in obese adults

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Figure 4: The relation between STBD\textsubscript{min}/STMD\textsubscript{min} and weight in 67 women with food allergy. The symbols as in Figure 1 and 2.

Discussion

To our knowledge, this is the first study investigating the possible influence of BMI and height on the risk of i.o./p. and SC injection in adult men and women, using the currently available EAlS.

A majority of both men and women would have a low risk of i.o./p. However, those with a low weight and BMI less than 20 kg/m2 had some risk of i.o/p injection using HPEAlS.

Importantly, the risk of SC injection was high, especially when injecting with HPEAlS through thick clothes, when injecting obese women through thick clothes at 100%. Using LPEAI\hspace{1em}S there was no risk of i.o./p injection, but there was some risk of subcutaneous injection especially in obese and overweight women. As illustrated in figure 4 and 5, obese women weighing more than 80 kg would not have any problems with longer than presently available needles up to 36 mm using LPEAI (=$\text{STBD}_{\text{min}}$) (7), corresponding to STMD\textsubscript{min} 34 mm, and STMD\textsubscript{min} with thick clothes, 31 mm.

As illustrated in figure 3 and 5, HPEAlS with longer needles with STBD\textsubscript{max} 25 mm, STMD\textsubscript{max} 23 mm and STMD\textsubscript{max} when injecting through thick clothes could possibly be of value. In Figure 5 is illustrated that using such a long needle would not cause any i.o./p. injections. Still, most overweight and all except two obese patients would obtain S.C. injections. So longer needle with maintained high pressure for release of the needle does not solve the problem.

These results suggest that manufacturers should introduce LPEAlS with longer needles that would reduce the risk for SC injection in obese and overweight women.
Figure 5: Presently available needle lengths and accepted needle length variation. Since the variation in needle length was 5 mm, lengths 18 and 13 mm represents STBD injection through naked skin, and 15 and 10 mm injection through thick clothing. The same applies to STMD distances; 16 and 11 mms apply to naked skin and 13 and 8 mms to thick clothing. In the heading of each table is given the number of patients and within brackets, the number of patients per BMI class: <25 kg/m², 20–25 kg/m², 25–30 kg/m², >30 kg/m². In the tables are given the number of patients per BMI class and within brackets the percentages. The colors are those used for grading, see statistics. Numbers in bold indicate 50% or more. The risk of i.o./p. injection is of importance only using long needles and the risk of SC injection most important using short needles.

Body mass index is not used in routine medical practice for prescribing EAs. However it has been proposed that the use of BMI would be a better instrument than weight and age (used in the UK) for selection of EAs for treatment of anaphylaxis in the community. To avoid SC injection (7) without an increased risk of i.o./p. injection using LPEAs, BMI can be used for selection of patients needing longer needles than presently available, Figure 5, right figures.

Weight and BMI were closely related. However, it is difficult to use among children and adolescent who are still growing. Furthermore, it seems BMI does not discriminate better but may function as a discriminator. In practice, we think our results, if confirmed indicates that obese adults would benefit from longer needles than those available at present.

With both HPEAs and LPEAs, height does not seem to be of any value to discriminate between those at risk and those not at risk neither for SC injection nor for i.o./p. injection.
As reported both ore rapid absorption of epinephrine than
®
influence of the variation in pressure on STMD and
2). 
53
required to trigger EAIs specifications. There is a significant variation of pressure allowed for batch release according to the manufacturers investigation, we did not know the variation in pressure and within brackets the percentages. The colors are those used for grading, see statistics. Numbers in bold indicate 50% or more. The risk of i.o./p. injection is of importance only using long needles and the risk of SC injection most important using short needles.

Table 5: Presently available needle lengths and accepted needle length variation. Since the variation in needle length was 5 mm, lengths 18 and 13 mm represents STBD injection through naked skin, and 15 and 10 mm injection through thick clothing. The same applies to STMD distances; 16 and 11 mms apply to naked skin and 13 and 8 mms to thick clothing. In the heading of each table is given the number of patients and within brackets, the number of patients per BMI class: <25 kg/m², 25-29.9 kg/m², 30-34 kg/m², >34 kg/m². In the tables are given the number of patients per BMI class and within brackets the percentages. The colors are those used for grading, see statistics. Numbers in bold indicate 50% or more. The risk of i.o./p. injection is of importance only using long needles and the risk of SC injection most important using short needles.

| Men, n = 32 (n/BMI class 3/9/12/8) |
|-------------------------------------|
| Naked skin | Thick clothing |
| STBD mm |
| STBDmax 10.0 | Lower limit | 0/0/0/0 |
| STBDmax 13.0 | | 1/0/0/0 (33/0/0/0) |
| STBDmax 15.0 | Upper limit | 1/0/0/0 (33/0/0/0) |
| STBDmax 18.0 | | 1/0/0/0 (33/0/0/0) |
| | STMD mm |
| STMDmax 8.0 | Lower limit | 0/0/3/4 (0/0/25/31) |
| STMDmax 11.0 | | 0/0/0/2 (0/0/25) |
| STMDmax 13.0 | Upper limit | 0/0/0/1 (0/0/13) |
| STMDmax 16.0 | | 0/0/0/0 |

Table 5A: The risk of i.o./p. and SC or i.o./p. injection using HPEAIs (Epipen®) in adult men. Presently available needle lengths.

Our data have one drawback. At the time of the original investigation, we did not know the variation in pressure allowed for batch release according to the manufacturers specifications. There is a significant variation of pressure required to trigger EAIs of more than six times, from 8.5 to 53 N Table 2 (11) that was not considered in this study (Table 2). Therefore, new studies should be completed to reveal the influence of the variation in pressure on STMD and STBD.

Table 5A2: Possible longer needles to avoid SC injection in obese women. The same variation but a one-inch needle, 25 mm.

We would also remind readers that other health sectors and specialties have other approaches with their injectors (15). Autoinjectors (AI) intended for injection of pharmaceuticals for the treatment of migraines are designed to perform a SC injection. They require far lower pressure on the AI, 6-13 N, and use shorter needles than are used in EAIs presently available. It should also be noted that the Centers for Disease control and prevention recommends a needle length of 25.4 mm (1 inch) for children 3 years and older and needles 25.4 – 38.1 mm for persons weighing 70 kg and more (16) for intramuscular injections.

| Men, n = 32 (3/9/12/8) |
|-------------------------|
| | Thick clothing |
| STBD mm |
| STBDmax 18.0 | Lower limit | 1/0/0/0 (33/0/0/0) |
| STBDmax 20.0 | | 1/0/0/0 (33/0/0/0) |
| STBDmax 23.0 | Upper limit | 3/3/1/0 (100/93/80) |
| STBDmax 25.0 | | 3/3/4/1 (100/93/80) |
| | STMD mm |
| STMDmax 15.0 | Lower limit | 0/0/0/0 |
| STMDmax 18.0 | | 0/0/0/0 |
| STMDmax 20.0 | Upper limit | 0/0/0/0 |
| STMDmax 23.0 | | 0/0/0/0 |

It has been claimed that IM injection is needed to obtain rapid distribution of epinephrine in the body (14, 17, 18). However, new studies should be completed, to convincingly show that IM injection is superior to SC injection. For now, we must assume the conclusions of Simons (18) and Duvauchelle (14) are correct. Recently, Worm et al. (12) hypothesized that the high force used by the HPEAI Epipen® would cause a more rapid absorption of epinephrine than injection with syringe and needle. However, this is just an hypothesis without any proof. It comes from their report that Epipen® injections are given subcutaneously due to the short needle. Despite that, the Cmax was reported both higher and earlier than injecting with syringe and needle.
### Table 5B: The risk of i.o./p. and SC or i.o./p. injection using LPEAIs (Emerade®) in adult men. Presently available needle lengths and accepted needle length variation.

| STBD mm |  | Naked skin | Thick clothing |
|---------|---|-------------|----------------|
| STBD_{min} 19.1 | Lower limit | 0/0/0/0 |
| STBD_{min} 20.6 | Upper limit | 0/0/0/0 |
| STBD_{min} 22.1 | Lower limit | 0/0/0/0 |
| STBD_{min} 23.6 | Upper limit | 0/0/0/0 |

| STMD mm |  | Naked skin | Thick clothing |
|---------|---|-------------|----------------|
| STMD_{min} 17.1 | Lower limit | 0/0/0/0 |
| STMD_{min} 18.6 | Upper limit | 0/0/0/0 |
| STMD_{min} 20.1 | Lower limit | 0/0/0/0 |
| STMD_{min} 21.6 | Upper limit | 0/0/0/0 |

### Table 5C: The risk of i.o./p. and SC injection using HPEAIs (Epipen®) in adult women. Presently available needle lengths and accepted needle length variation.

| STBD mm |  | Naked skin | Thick clothing |
|---------|---|-------------|----------------|
| STBD_{max} 10.0 | Lower limit | 0/0/0/0 |
| STBD_{max} 13.0 | Upper limit | 0/0/0/0 |
| STBD_{max} 15.0 | Upper limit | 1/0/0/0 |

| STMD mm |  | Naked skin | Thick clothing |
|---------|---|-------------|----------------|
| STMD_{max} 8.0 | Lower limit | 5/15/20/17 |
| STMD_{max} 11.0 | Upper limit | 1/7/16/15 |
| STMD_{max} 13.0 | Upper limit | 1/3/13/14 |

### Table 5B2: Possible longer needles to avoid SC injection in obese women. The same variation but a one-inch needle, 25 mm.

| STBD mm |  | Naked skin | Thick clothing |
|---------|---|-------------|----------------|
| STBD_{min} 31.5 | Lower limit | 0/0/0/0 |
| STBD_{min} 33.0 | Upper limit | 0/0/0/0 |
| STBD_{min} 34.5 | Lower limit | 0/0/1/0 |
| STBD_{min} 36.0 | Upper limit | 2/0/0/0 |

| STMD mm |  | Naked skin | Thick clothing |
|---------|---|-------------|----------------|
| STMD_{min} 29.5 | Lower limit | 0/0/0/0 |
| STMD_{min} 31.0 | Upper limit | 0/0/0/0 |
| STMD_{min} 32.5 | Lower limit | 0/0/0/0 |
| STMD_{min} 34.0 | Upper limit | 0/0/0/0 |

### Table 5C2: Possible longer needles to avoid SC injection in obese women. The same variation but a one-inch needle, 25 mm.

| STBD mm |  | Naked skin | Thick clothing |
|---------|---|-------------|----------------|
| STBD_{max} 18.0 | Lower limit | 1/0/0/0 |
| STBD_{max} 20.0 | Upper limit | 1/1/0/0 |
| STBD_{max} 23.0 | Upper limit | 3/2/0/0 |

| STMD mm |  | Naked skin | Thick clothing |
|---------|---|-------------|----------------|
| STMD_{max} 15.0 | Lower limit | 0/0/7/11 |
| STMD_{max} 18.0 | Upper limit | 0/0/1/4 |
| STMD_{max} 20.0 | Upper limit | 0/0/1/4 |
Studies should be initiated, firstly, investigating whether epinephrine should be given subcutaneously or intramuscularly. Secondly, studying the effect of force on the absorption of epinephrine injected SC and IM. Thirdly, investigating the distribution of skin to muscle and skin to bone distances considering all possible variations such as of needle length, pressure and the footprint of different brands as suggested in previous papers (4, 6, 7, 19).

Until studies are available, we suggest that the STBD and STMD should be determined in all patients with ultrasound and well defined pressure on to probe with the foot-print of the EAI to be prescribed, before prescribing an EAI (4, 6, 7, 19), the STBD and STMD should be determined in all patients by ultrasound and well defined pressure on the probe with the foot-print of the EAI to be prescribed.

In summary, using HPEAs in overweight and obese men, there was some risk of SC injection, partly overcome by reducing the variation in needle length and overcome by using longer needles and or using less pressure on the EAI. In obese women, the majority would receive a SC injection. Using a one inch needle would partially overcome these issues. Using LPEAs in overweight and obese men, does not lead to significant risk of SC or i.o./p. injection. In overweight women there would be some risk of SC injection, and in obese women there would be a high risk of SC injection that would be largely overcome using a longer needle.

| Women, n = 67 (5/22/23/17) | Naked skin | Thick clothing |
|---------------------------|------------|----------------|
| **STBD mm**               |            |                |
| STBD<sub>min</sub> 19.1   | Lower limit| 0/0/0/0        |
| STBD<sub>min</sub> 20.6   | Upper limit| 0/0/0/0        |
| STBD<sub>min</sub> 22.1   | Lower limit| 0/0/0/0        |
| STBD<sub>min</sub> 23.6   | Upper limit| 0/0/0/0        |
| **STMD mm**               |            |                |
| STMD<sub>min</sub> 17.1   | Lower limit| 1/3/10/12      |
|                           |            | (20/12)        |
| STMD<sub>min</sub> 18.6   | Upper limit| 0/1/7/11       |
|                           |            | (0/0/1/)       |
| STMD<sub>min</sub> 20.1   | Lower limit| 0/0/4/8        |
|                           |            | (0/0/17)       |
| STMD<sub>min</sub> 21.6   | Upper limit| 0/0/2/6        |
|                           |            | (0/0/17)       |

**Table 5D**: The risk of i.o./p. and SC or i.o./p. injection using LPEAs (Emerade<sup>®</sup>) in adult women. Presently available needle lengths and accepted needle length variation.

**Clinical Trial registry**: The original study was registered.

**Funding**: None.

**Conflicts of interests**: Sten Dreborg and Gina Tsai have no conflict of interest. Harold Kim has been on the advisory boards for Kaleo and Pfizer.

**Financial disclosure statement**: Nothing to disclose.

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Received on 15-11-2019 Accepted on 06-12-2019 Published on 30-12-2019

DOI: https://doi.org/10.31907/2310-6980.2019.07.02

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