Epinephrine for the out-of-hospital (first-aid) treatment of anaphylaxis in infants: Is the ampule/syringe/needle method practical?

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Background: Little information is available about administration of an accurate epinephrine dose to infants experiencing anaphylaxis outside the hospital setting.
Objective: Our purpose was to perform a prospective, controlled study of (1) the time needed by parents to draw up an infant epinephrine dose from an ampule and (2) the dose accuracy.
Methods: We gave 18 parents written instructions and asked them to draw up epinephrine 0.09 mL. We timed them by means of a stopwatch and measured the epinephrine content (in micrograms) in each dose by using HPLC-UV. Eighteen resident physicians, 18 general duty nurses, and 18 emergency department nurses served as controls.
Results: The parents took significantly longer ($P < .05$) than the controls to draw up the dose; the mean (± SEM) times were 142 ± 13 seconds (range, 83-248) for the parents, 52 ± 3 seconds (range, 30-83) for the physicians, 40 ± 2 seconds (range, 26-71) for the general duty nurses, and 29 ± 0.09 seconds (range, 27-33) for the emergency department nurses. The control groups did not differ significantly from each other in speed ($P > .05$). The epinephrine content of the doses drawn up by the parents ranged 40-fold in contrast to the physicians' doses (7- to 8-fold), general duty nurses' doses (3-fold), and emergency department nurses' doses (2-fold). The mean epinephrine content did not differ significantly ($P > .05$) among the 4 groups.
Conclusions: Most parents were unable to draw up an infant epinephrine dose rapidly or accurately. Most health care professionals drew up the dose rapidly; however, their accuracy was compromised by inherent variations of epinephrine concentrations in the ampules (*United States Pharmacopeia* compendial limits, 90% to 115%) and the inherent difficulty of measuring low volumes (<0.1 mL) of epinephrine. User-friendly premeasured epinephrine doses suitable for infants should be developed. (J Allergy Clin Immunol 2001;108:1040-4.)

Key words: *Epinephrine, adrenaline, systemic anaphylaxis, acute allergic reaction, infants, first aid, EpiPen, Ana-Kit*

Abbreviation used
USP: *United States Pharmacopeia*

Information about administering an accurate epinephrine dose of 0.01 mg/kg to infants experiencing anaphylaxis outside the hospital setting is conspicuously absent from textbooks,[1-8] consensus statements,[9,10] and formularies.[11,12] In a recent administrative claims review of epinephrine dispensings for out-of-hospital use during a 4-year period, we found that epinephrine was dispensed for 1.2% of a pediatric population comprising almost 280,000 infants, children, and adolescents.[13] The EpiPen Jr, which delivers a fixed, premeasured sterile dose of 0.15 mg, was dispensed for infants as young as age 2 months. The Ana-Kit (no longer manufactured[11,12]), which delivered doses of 0.05, 0.1, 0.15, 0.2, or 0.3 mg, was dispensed for infants as young as 4 months. Epinephrine ampules, from which it is theoretically possible to administer a precise epinephrine dose on a milligram-per-kilogram basis, were dispensed for infants as young as age 2 months, and though infrequently dispensed overall, accounted for 20% of the total epinephrine dispensings for infants.

Currently, physicians must choose between 2 alternatives for infant outpatients at risk for anaphylaxis: prescribing a user-friendly EpiPen Jr (0.15 mg) and potentially overdosing the infant, or prescribing an epinephrine ampule along with a sterile syringe/needle and instructions. The question has been raised, "When hands are shaking and a needle is exposed, will nervous parents end up dosing epinephrine from an ampule correctly?"[14] In developing a teaching module for the parents of such infants, we found that there were no published data with regard to speed and accuracy of epinephrine dosing with the ampule/syringe/needle technique.

We hypothesized that parental use of the epinephrine ampule/syringe/needle method for drawing up an infant epinephrine dose might lead to a delay in dosing and to inaccurate dosing. In a prospective, controlled study, we instructed parents of children at risk for anaphylaxis in the method of drawing up an infant epinephrine dose of 0.09 mg (0.09 mL) into a syringe. We timed their ability to draw up the dose and assessed the accuracy of the dose

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by measuring the amount of epinephrine in it by using an HPLC technique. Resident physicians, general duty nurses, and emergency department nurses served as controls.

METHODS

This project was reviewed by the Research Ethics Board of the University of Manitoba. The study was performed at the Children's Hospital/Health Sciences Center and the John Buhler Research Center, Winnipeg, Manitoba, Canada.

Participants

In the Allergy Clinic, we tested a convenience sample of 18 consecutive parents of highly allergic children with histories of anaphylaxis. During previous clinic visits, each parent had been instructed on how to inject epinephrine by means of an EpiPen Jr or an EpiPen; however, none of them had experience with a needle and syringe and none had ever been shown how to draw up epinephrine from an ampule. Parents with a medical background (eg, physicians, nurses, and pharmacists) were excluded from participation. We also tested 3 control groups of Children's Hospital health care professionals: 18 pediatric residents with at least 3 months of training, 18 general duty nurses, and 18 emergency department nurses. All parents and controls were fluent in the English language. No one was notified in advance about his or her involvement in the project, and no one was allowed to practice.

Demonstration of epinephrine injection by using the ampule/syringe/needle technique

Parents and controls received the same scripted introduction to the demonstration. They were advised that the objective was to facilitate the development of a teaching module for parents of infant outpatients at risk for anaphylaxis for whom the EpiPen Jr did not deliver an optimally low dose and that (1) the outcomes—speed and accuracy—would be evaluated by group, (2) testing would be anonymous (ie, their names would not be recorded), and (3) they could refuse to participate or could stop participating at any time.

Each participant, tested individually, was presented with an identical simulated emergency situation, as follows: "Please demonstrate how you would measure 0.09 mL of epinephrine 1/1000 from this ampule for injection into a 9-kg baby experiencing anaphylaxis; then inject the dose into the vial provided. On the picture diagram, show where the epinephrine should be injected." The rationale for selecting a 0.09-mL test dose was that this is the recommended dose for a 9-kg infant[1-11] and 9 kg is the 50th percentile weight for an infant 9 to 10 months old[15]—a typical age of presentation with a first severe allergic reaction to a food.

Each participant was given a 1-mL disposable plastic "tuberculin" syringe with graduated 0.01-mL markings and an attached 27-gauge ½-inch length SlipTip needle (Becton Dickinson & Co, Franklin Lakes, NJ), a 1-mL glass ampule of epinephrine USP (1:1000 [1 mg/mL]; Abbott Laboratories, Ltd, Saint-Laurent, Quebec, Canada), a 10-mL sterile, rubber-stoppered dosing vial, and an alcohol swab. The 72 different epinephrine ampules used in the study were purchased from the Health Sciences Center pharmacy, came from 8 different lot numbers, and were used within 3 to 16 months of the expiration date.

Explicit step-by-step written instructions with regard to opening the ampule, removing air from the syringe, and measuring the correct volume of epinephrine were reviewed with each parent individually (Table I), and the parents had the opportunity to discuss the procedure. The controls were not given any instructions apart from the scripted introduction and the simulated emergency described previously, because it was expected that health care professionals would know how to draw up a dose of medication for injection.

TABLE I. Instructions for parents/caregivers: How to draw up an infant dose of epinephrine

1. Tap epinephrine ampule to make sure liquid is at the bottom.
2. Snap top off ampule (carefully!).
3. Remove sterile syringe with attached needle from package.
4. Take cap off needle.
5. Put needle tip in epinephrine and pull up liquid.
6. Hold needle point up and syringe down, then tap air out of syringe.
7. Measure the epinephrine dose of 0.09 mL exactly.
8. Inject the epinephrine.

Participants were allowed to begin the demonstration whenever they were ready. By means of a stopwatch, they were timed from the moment they picked up the epinephrine ampule or the wrapped, sealed, sterile syringe/needle unit to the moment they completed the epinephrine injection into the vial. Indicating the appropriate injection site on the diagram of an unclothed small child was not timed.

A checklist was used to monitor the following: technique for glass ampule breaking, removal of air from the syringe, and measurement of an accurate volume for injection on the basis of visual inspection of the syringe. Participants' comments were recorded verbatim.

The vials containing the epinephrine were labeled by study group (parent, physician, general duty nurse, or emergency department nurse), protected from light, and frozen at –20°C within 4 hours. Later, the contents were thawed and exactly 10 mL distilled water was pipetted into each vial, which was then recapped and gently inverted and rotated to ensure that the entire epinephrine dose was uniformly distributed into the water. An aliquot of the solution was then removed for epinephrine quantitation by using a specific, sensitive HPLC method with UV detection at 280 nm (*United States Pharmacopeia* [USP] method).[16] The volume of epinephrine was calculated by using a normalized epinephrine concentration of 90 μg/0.09 mL (0.09 mg/0.09 mL), since each participant used a different epinephrine ampule and the ampules contained 90% to 115% epinephrine (USP compendial limits).

The mean differences in number of seconds needed to draw up the epinephrine and in epinephrine content (in micrograms) among the 4 different groups were compared by using ANOVA and the Tukey and Bonferroni multiple range tests (performed by means of PC-SAS). Differences were considered to be significant at $P \leq .05$.[17]

RESULTS

Eighteen parents of children at risk for anaphylaxis agreed to take part in the project, as did 18 pediatric resident controls, 18 general duty nurse controls, and 18 emergency department nurse controls. All 72 participants completed the study.

In contrast to the health care professionals, all of whom demonstrated the correct technique for opening the glass ampule, drawing up the epinephrine into the syringe, and removing the air from the syringe, 3 of 18 parents struggled to open the ampule and 1 parent inadvertently shattered it, narrowly escaping injury from glass shards. Four parents experienced difficulty in getting the air out of the syringe. In addition, 3 parents were unable to indicate the correct site for epinephrine injection using the diagram.

The parents took a significantly longer time ($P \leq .05$) to draw up the epinephrine dose than the controls did (Fig 1). The mean (± SEM) values for elapsed time from

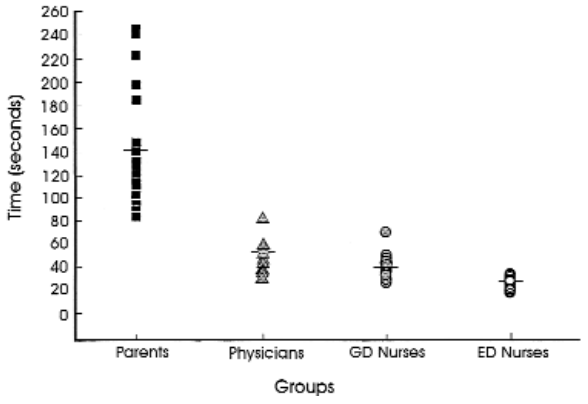

FIG 1. The length of time needed for participants to draw up the epinephrine dose is shown by group. The parents were significantly slower ($P \leq .05$) than the controls. During treatment of actual anaphylaxis, when seconds count, this difference might be clinically relevant. The controls did not differ significantly from each other ($P > .05$). *GD,* General duty; *ED,* emergency department.

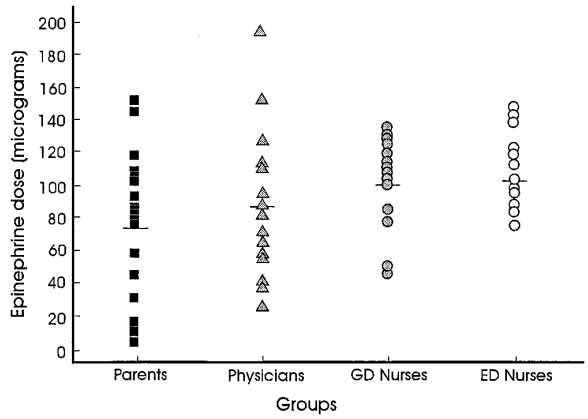

FIG 2. The epinephrine content (in micrograms) of the dose drawn up by the participants is shown by group. Wide variances were found, from a 40-fold range in epinephrine content of parents' doses (worst) to a 2-fold range of epinephrine content of emergency department nurses' doses (best). The mean epinephrine doses drawn up by each group did not differ significantly ($P > .05$). *GD,* General duty; *ED,* emergency department.

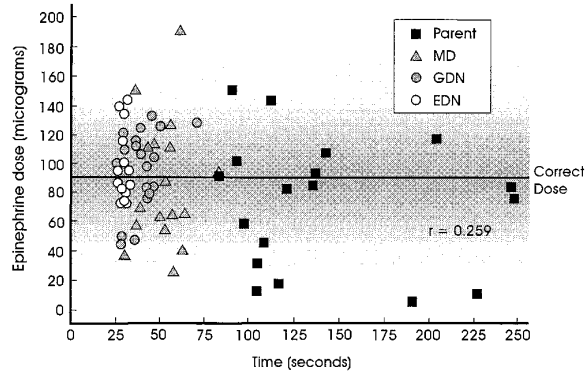

FIG 3. There was no correlation between the accuracy of the epinephrine dose and the speed with which the dose was drawn up. It is a concern that some doses fell outside the potential 50% underdosing (45 μg) and 50% overdosing (135 μg) broad limits indicated by the *shaded areas. MD,* Physician; *GDN,* general duty nurse; *EDN,* emergency department nurse.

picking up the syringe to injecting the epinephrine dose into the vial were as follows: parents, 142 ± 13 seconds (range, 83-248); physicians, 52 ± 3 seconds (range, 30-83); general duty nurses, 40 ± 2 seconds (range, 26-71); and emergency department nurses, 29 ± 0.09 seconds (range, 27-33). The control groups did not differ significantly from each other with regard to speed ($P > .05$).

The mean (± SEM) volume of epinephrine drawn up by the parents was 0.07 ± 0.01 mL (range, 0.004-0.151); this compared with volumes of 0.085 ± 0.01 mL (range, 0.03-0.19) for the physicians, 0.098 ± 0.01 mL (range, 0.04-0.13) for the general duty nurses, and 0.099 ± 0.01 mL (range, 0.07-0.15) for the emergency department nurses.

The mean (± SEM) value for epinephrine content of the parents' doses (73 ± 11 μg; range, 4-151) did not differ significantly from those of the physicians (86 ± 10 μg; range, 25-193), the general duty nurses (98 ± 7 μg; range, 44-133), or the emergency department nurses (99 ± 6 μg; range 72-145; $P > .05$; Fig 2). There was an almost 40-fold range of epinephrine content of the doses drawn up by the parents; this was in contrast to a 7- to 8-fold range in the physician group, a 3-fold range in the general duty nurse group, and a 2-fold range in the emergency department nurse group.

There was no correlation between the time that it took to draw up the epinephrine doses and the amount of the epinephrine (in micrograms) contained in the doses (Fig 3). The parents' comments about the technique included the following:

"It takes too long."
"The components are small and easy to lose."
"The amount is tiny, impossible to remember, and difficult to measure."
"It is very easy to give an overdose or no dose at all."
"The removal of the air is the hardest part."
"This is way too much to ask of a parent."
"In a real-life emergency, an anxious parent could not do this."
"This is far too hard, too complicated, and too difficult for a parent to do."
"Babysitters and daycare staff would refuse to do this."

DISCUSSION

The available options for administration of an accurate epinephrine dose to infants experiencing anaphylaxis outside the hospital setting vary considerably in ease of use and in cost, and each has advantages and disadvantages.

The EpiPen Jr and EpiPen auto-injectors currently represent the most user-friendly method of giving an epinephrine injection, but they are also associated with the greatest expense ($50.00 US or more for a single dose) and are not available in many countries. They have the additional disadvantage that neither of the 2 doses available (0.15 mg for the EpiPen Jr and 0.3 mg for the EpiPen) is suitable for infants, given that even by the age of 24 months only 3% of infants will have achieved a weight of 15 kg.[15] The Ana-Kit was intermediate between the EpiPen Jr and EpiPen auto-injectors and the

epinephrine ampule/syringe/needle technique in terms of both user-friendliness (an infant epinephrine dose of 0.05 or 0.1 mg could be marked by using adhesive tape or indelible ink) and cost ($30.00). The epinephrine ampule/syringe/needle technique that we studied is the least user-friendly method but also the least expensive, costing approximately $1.00. It has the theoretical advantages that accurate dosing can be made on a milligrams-per-kilogram basis and that repeat doses, which are needed by more than one third of patients experiencing anaphylaxis,[18] can be given. In addition to the disadvantage demonstrated in this study—namely, that parents have difficulty with the technique—it also has the disadvantage that epinephrine in clear glass ampules is not protected from light and might readily oxidize to adrenochrome and melanin.[16]

We found that even in a simulated emergency situation, which did not incorporate the shaking hands, nervousness,[14] and/or panic that might be present if they actually had to give an injection to their infant, most parents had difficulty in drawing up an epinephrine dose rapidly and accurately. The "fastest" parent was "slower" than all but one of the health care professionals, and the magnitude of the delays might be relevant in the treatment of anaphylaxis, which is a true emergency.[19] Many of the parents felt uncomfortable with the technique and found it difficult to remove the air from the syringe.

We have also shown that parents had difficulty in drawing up a low dose of epinephrine accurately, with a 40-fold variation of epinephrine content of dose in this group. In contrast, variations ranged from 7- to 8-fold in the physician control group to 2- to 3-fold in the nurse control groups. In the interpretation of this data, it cannot be assumed that each and every epinephrine dose of 0.09 mL contained precisely 90 μg of epinephrine. The epinephrine ampules used in the study were within 3 to 16 months of their expiration date, and given that the USP compendial limits for the epinephrine content of the ampules are 90% to 115% of the labeled strength, a dose of 0.09 mL measured correctly from an ampule might therefore legitimately have contained from 81 to 104 μg epinephrine, depending on whether the ampule used was close to its expiration date or not. In addition, accurate measurement of liquids requires appropriate equipment, and the accuracy of widely available disposable plastic "tuberculin" syringes, though ±5% at a volume of 1 mL, might be considerably more than ±5% when volumes of less than 0.1 mL are being measured.[20] Precision in dosing is important for all medications; however, it is critical for those such as epinephrine, which have a narrow therapeutic/toxic ratio.[21]

In summary, in this prospective, controlled study, we have clearly demonstrated that the low-cost, "low-tech" epinephrine ampule/syringe/needle technique is not practical for use by parents of infants experiencing anaphylaxis outside the hospital setting. Although caregivers could be taught to improve their speed and accuracy and regular reeducation sessions could be given, it is unlikely that many parents would be motivated to practice their technique regularly in preparation for an event that might never occur. Currently, for the first-aid treatment of anaphylaxis in infants, the goals of precise epinephrine dosing of 0.01 mg/kg and user-friendly, rapid epinephrine injection are mutually exclusive. Prescribing the EpiPen Jr for use in infants—though it is certainly not ideal, because it delivers a 3-fold epinephrine overdose to those weighing approximately 5 kg and a 2-fold epinephrine overdose to those weighing approximately 7.5 kg—appears to be a preferable alternative to the epinephrine ampule/syringe/needle technique. Use of the latter might lead not only to an overdose but also to a suboptimal dose to no dose at all, or to a delay in dosing. Additional premeasured or pharmacy preset sterile epinephrine doses of 0.05 mg and 0.1 mg in user-friendly formulations are urgently needed.

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