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## First-aid treatment of anaphylaxis to food: Focus on epinephrine

F. Estelle R. Simons, MD, FRCPC Winnipeg, Manitoba, Canada

Avoiding food triggers for anaphylactic reactions (severe acute systemic allergic reactions) is easier said than done. Most episodes of anaphylaxis to food occur unexpectedly in the community in the absence of a health care professional. All individuals at risk should therefore have an emergency action plan in place. The cornerstone of first-aid treatment of anaphylaxis is epinephrine injected intramuscularly in the vastus lateralis muscle (lateral aspect of the thigh). In this review, we focus on epinephrine. We examine a therapeutic dilemma: the issue of epinephrine dose selection in an individual for whom no optimal fixed-dose auto-injector formulation exists, and a therapeutic controversy: the issue of epinephrine injection versus an oral H<sub>1</sub>-antihistamine in anaphylaxis episodes that appear to be mild. The pharmaceutical industry could address the first of these issues by providing a wider range of epinephrine fixed doses in easy-to-use auto-injectors, or by providing adjustable epinephrine doses in auto-injectors. The second issue could be addressed in part by development of alternative routes of epinephrine administration for the first-aid, out-of-hospital treatment of anaphylaxis. (J Allergy Clin Immunol 2004;113:837-44.)

**Key words:** Acute allergic reaction, adrenaline, adults, anaphylaxis, auto-injector, children, epinephrine, EpiPen, EpiPen Jr, food allergy, peanut allergy, H<sub>1</sub>-antihistamines, activated charcoal

Historically, anaphylaxis was triggered mainly by biological substances such as antitoxin or by medications, and usually occurred in a health care setting.<sup>1</sup> Currently, food is the most common trigger of anaphylaxis, and most episodes occur unexpectedly in the community in the absence of a trained health care professional.<sup>2,3</sup> Anaphylaxis is defined as an acute systemic allergic reaction that varies in severity from mild to life-threatening or fatal and may be rapidly progressive. Individuals who have had such a reaction (or for children, their caregivers) should be equipped with an anaphylaxis emergency action plan<sup>4-6</sup> and with injectable epinephrine for first-aid treatment,<sup>6-9</sup> defined as treatment before or during transport to an emergency department.

Here, we review the current scientific evidence on which the first-aid treatment of anaphylaxis is based. We focus chiefly on epinephrine and address 2 difficult issues

### Abbreviation used

t<sub>max</sub>: Time to peak plasma concentration

in first-aid treatment with this life-saving medication: the dilemma of epinephrine dose selection in individuals for whom no optimal fixed-dose auto-injector formulation exists, and the controversial issue of epinephrine injection versus an oral H<sub>1</sub>-antihistamine in anaphylaxis episodes that appear to be mild.

## EPINEPHRINE IN THE FIRST-AID TREATMENT OF ANAPHYLAXIS

### Pharmacologic activity

Epinephrine is a direct-acting sympathomimetic  $\alpha$ -adrenergic and  $\beta$ -adrenergic agonist with cyclic adenosine monophosphate-mediated, complex, bidirectional pharmacologic effects on many target organs<sup>10</sup> (Fig 1). Achieving high plasma and tissue epinephrine concentrations rapidly appears to be critical for reversal of hypotension<sup>11</sup> and possibly for survival. Epinephrine has a narrow toxic-therapeutic index (risk-to-benefit ratio). Administered to individuals of any age, in therapeutic doses, by any route, including inhalation, it may cause pharmacologic adverse effects such as anxiety, fear, restlessness, headache, dizziness, palpitations, pallor, and tremor.<sup>12,13</sup> Rarely, and especially after overdose, it may lead to ventricular arrhythmias, angina, myocardial infarction, pulmonary edema, sudden sharp increase in blood pressure, and intracranial hemorrhage. The risk of epinephrine adverse effects may be increased in individuals with some pre-existing cardiovascular, central nervous system, or thyroid diseases; in persons using monoamine oxidase inhibitors, which block epinephrine metabolism; or in those using tricyclic antidepressants or cocaine, in whom epinephrine duration of action is prolonged.<sup>12</sup> There is, however, no absolute contraindication to epinephrine use in anaphylaxis.

### Evidence base for epinephrine use in anaphylaxis

Recommendations for epinephrine dosing in the first-aid, out-of-hospital treatment of anaphylaxis are based on anecdotal experience and vary with regard to maximum initial dose (0.2 mg to 0.5 mg in adults; 0.01 mg/kg to a maximum of 0.3 mg in children), route of injection (subcutaneous vs intramuscular), and interval between doses (5-30 minutes).<sup>6-9</sup> Prospective, randomized, double-blind, placebo-controlled clinical trials of epinephrine in individuals actually experiencing anaphylaxis are

From the Section of Allergy and Clinical Immunology, Department of Pediatrics and Child Health; and the Department of Immunology, National Training Program in Asthma and Allergy, University of Manitoba, Winnipeg, Manitoba, Canada.

Received for publication January 15, 2004; revised January 15, 2004; accepted for publication January 18, 2004.

Date first published: May 7, 2004; date retracted: May 21, 2004; date republished: May 25, 2004.

Reprint requests: F. Estelle R. Simons, MD, FRCPC, Children's Hospital of Winnipeg, 820 Sherbrook Street, Winnipeg, Manitoba, Canada R3A 1R9; E-mail: lmcniven@hsc.mb.ca.

0091-6749/\$30.00

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doi:10.1016/j.jaci.2004.01.769

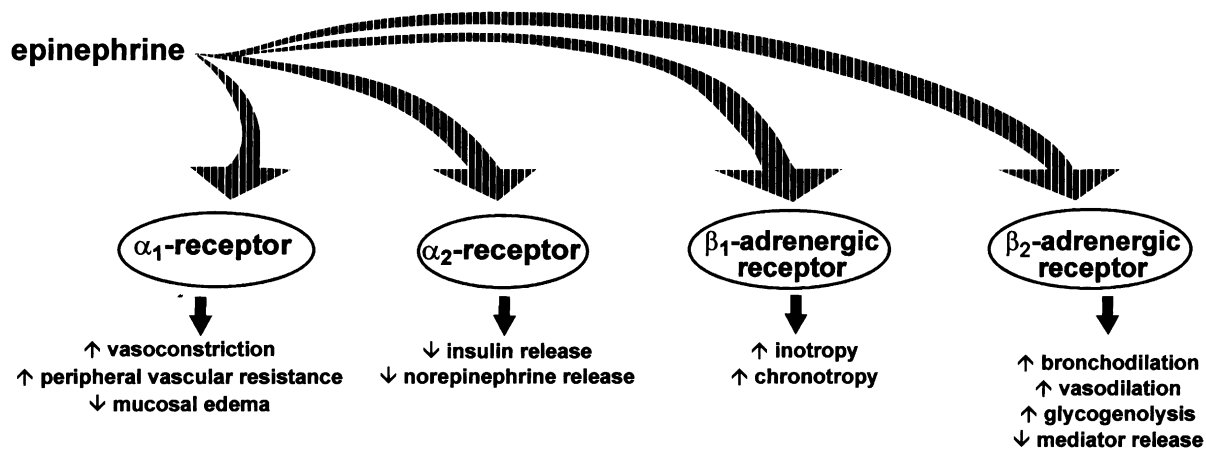


**FIG 1.** Pharmacology of epinephrine. In anaphylaxis, epinephrine's  $\alpha_1$ -adrenergic effects (vasoconstriction, increased peripheral vascular resistance, and decreased mucosal edema) and some of its  $\beta_2$ -adrenergic effects (bronchodilation and decreased mediator release from mast cells and basophils) are of primary importance. Low epinephrine concentrations may paradoxically enhance release of histamine and other mediators from mast cells and basophils and result in vasodilation.<sup>10</sup>

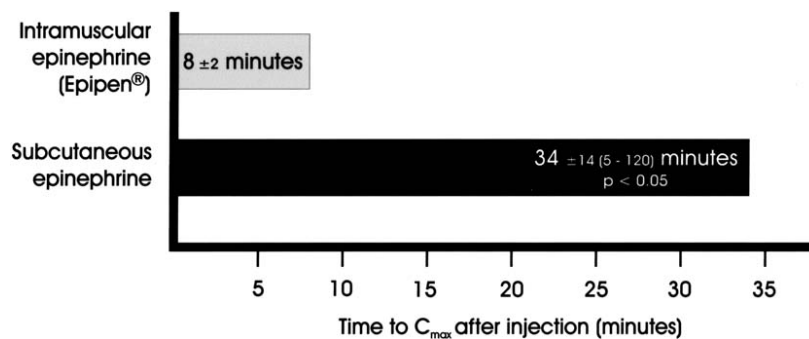


**FIG 2.** Absorption of epinephrine is faster after intramuscular injection than after subcutaneous injection. In a prospective, randomized, blinded study in children, the  $t_{max}$  was 8 ± 2 minutes after injection of epinephrine 0.3 mg from an EpiPen intramuscularly in the vastus lateralis. In contrast, the time to  $t_{max}$  was 34 ± 14 minutes (range, 5 to 120) after injection of epinephrine 0.01 mg/kg subcutaneously in the deltoid region. Based on data from Simons et al.<sup>14</sup>

unethical because prompt treatment with epinephrine is deemed critically important for survival. Also, such studies would be difficult to conduct because anaphylaxis episodes usually occur without warning in a nonmedical setting and differ in severity among individuals and from one episode to another in the same individual; consequently, baseline measurements and frequent timed measurements would be hard to obtain.

Despite the absence of clinical trials, evidence from clinical pharmacology studies, epidemiologic studies, and other investigations supports the use of epinephrine in anaphylaxis.<sup>6-9</sup> Based on the observation that subcutaneous administration of epinephrine causes skin blanching at the injection site as a result of the powerful  $\alpha_1$  vasoconstrictor effect of the drug, it was hypothesized that retention of epinephrine at the site of subcutaneous injection might lead to a delay in absorption into the systemic circulation. This hypothesis was initially tested in a randomized, blind study in children at risk for anaphylaxis in whom the time to peak plasma epinephrine concentration ( $t_{max}$ ), accompanied by prompt physiologic

effects, was 8 ± 2 minutes after intramuscular injection, significantly shorter than the  $t_{max}$  of 34 ± 14 minutes (range, 5 to 120) after subcutaneous injection<sup>14</sup> (Fig 2). The total amount of epinephrine eventually absorbed did not differ significantly. These findings were confirmed and extended in a randomized, blind, placebo-controlled, 6-way crossover study of epinephrine 0.3 mg (0.3 mL) intramuscular versus subcutaneous injection in young adults.<sup>15</sup> Peak plasma epinephrine concentrations were significantly higher ( $P < .01$ ) after epinephrine injection in the vastus lateralis muscle, attributed to its large size and excellent blood supply, compared with epinephrine injection in the deltoid muscle, epinephrine injection subcutaneously in the deltoid region, or placebo injection.

### Limitations of epinephrine first-aid treatment in anaphylaxis

Epinephrine is usually, but not always, effective in the first-aid treatment of anaphylaxis. Many potential reasons for lack of response can be identified<sup>7,9,13-20</sup> (Table I). These include rapid progression of the episode, and failure

**TABLE I.** Potential reasons for lack of response to epinephrine in anaphylaxis

|                                                                                                                                                         | Relevant studies                                                      | Comments                                                                                                                                                                       | References |
|---------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Patient/caregiver/physician                                                                                                                             |                                                                       |                                                                                                                                                                                |            |
| Rapid anaphylaxis progression                                                                                                                           | Case reports, autopsy reports                                         | In 10% of anaphylaxis episodes, epinephrine does not work even if given promptly                                                                                               | 25-28      |
| Epinephrine given too late                                                                                                                              | Case reports, autopsy reports                                         | Cause-and-effect hard to prove                                                                                                                                                 | 25-28      |
| Individuals do not know how to use epinephrine auto-injectors                                                                                           | Cross-sectional surveys, demonstrations                               | Frequently reported                                                                                                                                                            | 7-9,16     |
| Epinephrine-related                                                                                                                                     |                                                                       |                                                                                                                                                                                |            |
| Dose too low                                                                                                                                            | Few dose-response studies                                             | Optimal dose unknown; based on tradition, 0.3 mg is used for adults in many countries, 0.5 mg in some countries                                                                | 7-9,13     |
| Lack of availability of fixed doses 0.05, 0.1, 0.2, 0.25 mg in auto-injectors                                                                           |                                                                       | Impossible to give an appropriate dose to infants and to some young children                                                                                                   | 12         |
| Route/site not optimal                                                                                                                                  | Intramuscular vs subcutaneous*                                        | Intramuscular, thigh preferred to subcutaneous, arm                                                                                                                            | 14,15      |
|                                                                                                                                                         | Ampule and syringe*                                                   | Non-medical personnel lack speed and accuracy                                                                                                                                  | 18         |
|                                                                                                                                                         | Pressurized metered-dose inhaler†                                     | For systemic effects, adults need 20-30 puffs (children 10-20); possible phase-out by 2006                                                                                     | 17         |
| Past expiration date                                                                                                                                    | Bioavailability measured in animal models; content measured in vitro‡ | Epinephrine content inversely related to number of months past expiration date                                                                                                 | 19         |
| Other                                                                                                                                                   |                                                                       |                                                                                                                                                                                |            |
| Individual not supine                                                                                                                                   | Autopsy reports                                                       | If the individual is standing, venous return is decreased, the ventricles are empty, and death may occur despite timely epinephrine-induced reversal of vasodilation and shock | 31         |
| Individual taking medications ( $\beta$ -blocker or $\alpha$ -blocker, angiotensin-converting enzyme inhibitor) that prevent optimal epinephrine effect | Case reports                                                          | There is more information about lack of effect in asthma than in anaphylaxis                                                                                                   | 9          |
| Adverse effects of sodium metabisulfite (antioxidant in epinephrine)                                                                                    | Case reports                                                          | Additional studies needed, because sulfite-sensitive asthmatics tolerate epinephrine                                                                                           | 20         |

\*In obese individuals, intramuscular injections of epinephrine may inadvertently end up being subcutaneous injections unless a needle at least 2.5 cm (1 in) is used to penetrate the fat pad over the vastus lateralis muscle.<sup>23</sup>

†It is difficult to inhale the large number of epinephrine puffs required because of vasoconstriction of the oropharyngeal mucosa, causing tingling and burning sensations.<sup>17</sup>

‡Compendial limits for epinephrine content of formulations are 90% to 115% of labeled strength (United States Pharmacopeia),<sup>12</sup> but in some countries, the stated content of epinephrine in auto-injectors may range from 0.23 mg to 0.37 mg.<sup>21</sup> Epinephrine should be stored at room temperature (15°C to 30°C) to prevent oxidation and inactivation. In an EpiPen auto-injector, it is supplied in light-resistant packaging, and each 0.3-mL dose contains 0.3 mg epinephrine, 1.8 mg sodium chloride, 0.5 mg sodium metabisulfite, and hydrochloric acid to adjust the pH from 2.2 to 5.0. An EpiPen Jr contains epinephrine 0.15 mg and the same nonmedicinal ingredients in the same amounts as in the EpiPen.

to give epinephrine in a timely manner or to administer it correctly: in 1 survey, only 30% of individuals at risk for anaphylaxis to food, or their caregivers, could demonstrate how to use an auto-injector.<sup>16</sup> In addition, epinephrine may not be given in an optimal dose or administered by an optimal route. As noted previously, subcutaneous injection may lead to a delay in epinephrine absorption<sup>14,15</sup>; in addition, inhalation of a few puffs of epinephrine from a pressurized metered-dose inhaler will be inadequate for treatment of nonrespiratory symptoms,<sup>17</sup> and supplying individuals with an epinephrine ampule, syringe, and

needle may lead to delayed dose, overdose, underdose, or no dose at all.<sup>18</sup> In 1 study, parents without health care training who were instructed on how to draw up an infant dose of epinephrine from an ampule took significantly longer to get the dose into the syringe than physician or nurse controls did (Fig 3); moreover, the epinephrine content of the parents' doses ranged 40-fold, and their speed and accuracy did not correlate.<sup>18</sup>

Out-of-date EpiPen and EpiPen Jr auto-injectors (Dey, Napa, Calif) may not provide an optimal dose of epinephrine, even if their contents appear to be clear and with-

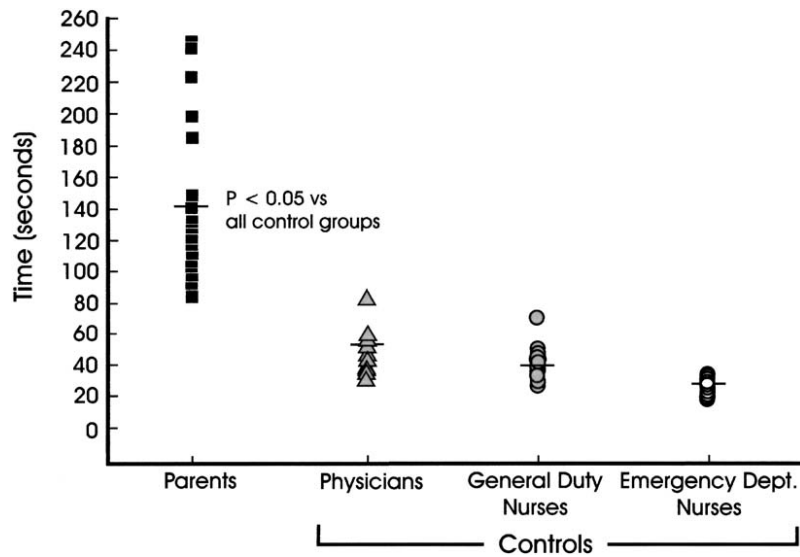


**FIG 3.** Individuals with no medical training have difficulty drawing up epinephrine from an ampule. In a prospective study, 18 parents, 18 resident physicians, 18 general duty nurses, and 18 emergency department nurses drew up an infant epinephrine dose from a 1-mL ampule. The parents required a mean time of  $142 \pm 13$  seconds (range, 83-248), significantly longer ( $P < .05$ ) than the control groups.<sup>18</sup>

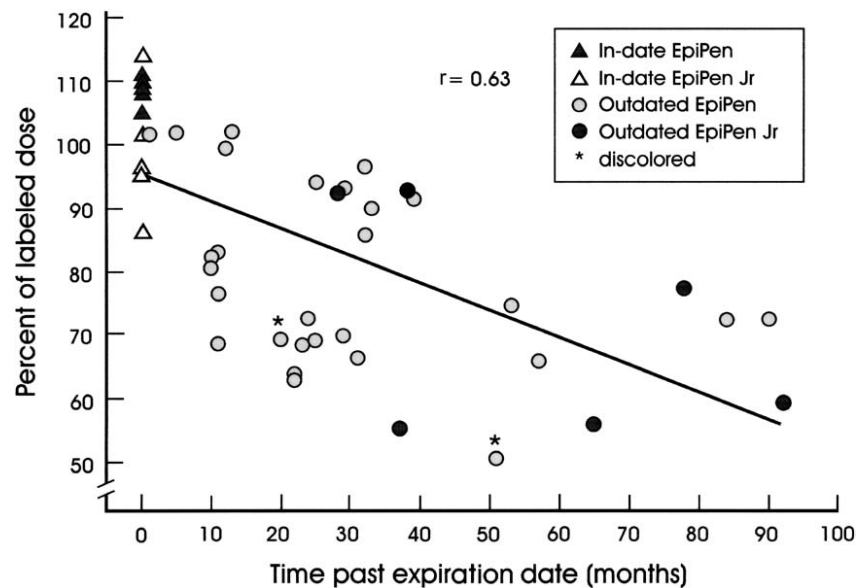


**FIG 4.** Use of an out-of-date epinephrine auto-injector may lead to injection of a suboptimal dose. Unused EpiPens and EpiPens Jr were studied 1 to 90 months after the expiration dates stated on the auto-injectors. The epinephrine content, measured by using a high-performance liquid chromatography-ultraviolet technique, correlated inversely with the length of time past the expiration date ( $r = 0.63$ ).<sup>19</sup>

out apparent pink or brown discoloration from oxidation of epinephrine to adrenochrome or melanin. Significant reduction in epinephrine bioavailability from out-of-date auto-injectors has been documented, and their measured epinephrine content correlates inversely with the length of time past the expiration date ( $r = 0.63$ )<sup>19</sup> (Fig 4).

Lack of an optimal range of epinephrine doses in easy-to-use auto-injectors for first-aid use, and lack of ability to adjust the epinephrine dose in auto-injectors, may also

contribute to underdosing with epinephrine and to lack of response in some individuals.

#### Epinephrine dose dilemma: 2 fixed-dose auto-injectors do not suffice

An important factor that needs to be addressed by regulatory agencies and ultimately by the pharmaceutical industry is the availability of only 2 fixed doses of epinephrine (0.15 mg and 0.3 mg) in easy-to-use

**TABLE II.** Clinical dilemma: Selecting an appropriate epinephrine fixed-dose auto-injector for infants and children

|                                                | Body weight                |                              |                         |                                                            |                                                            |                      |
|------------------------------------------------|----------------------------|------------------------------|-------------------------|------------------------------------------------------------|------------------------------------------------------------|----------------------|
|                                                | ≤5 kg                      | 10 kg                        | 15 kg                   | 20 kg                                                      | 25 kg                                                      | ≥30 kg               |
| Age at which this weight is 50th percentile    | 2 mo                       | 14 mo                        | 3 y                     | 6 y                                                        | 9 y                                                        | 12 y                 |
| Optimal epinephrine dose                       | 0.05 mg                    | 0.1 mg                       | 0.15 mg                 | 0.2 mg                                                     | 0.25 mg                                                    | 0.3 mg               |
| Is optimal dose available in an auto-injector? | No                         | No                           | Yes                     | No                                                         | No                                                         | Yes                  |
| Physician's dilemma,* if any                   | EpiPen Jr: 3-fold overdose | EpiPen Jr: 1.5-fold overdose | EpiPen Jr: optimal dose | EpiPen Jr: 1.3-fold underdose<br>EpiPen: 1.5-fold overdose | EpiPen Jr: 1.7-fold underdose<br>EpiPen: 1.2-fold overdose | EpiPen: optimal dose |
| Situation acceptable?                          | No                         | No                           | Yes, use EpiPen Jr      | No                                                         | No                                                         | Yes, use EpiPen      |

\*The difficulty of giving a precise epinephrine dose of 0.01 mg/kg to a child weighing <15 kg or weighing between 15 and 30 kg, either by using the EpiPen Jr (0.15 mg) or the EpiPen (0.3 mg), is outlined, including the magnitude of overdose or underdose that must be accepted if 1 of the currently available fixed-dose auto-injectors is recommended.

There is a possibility that underdosing (<0.01 mg/kg) may occur when some larger children, adolescents, and adults use the EpiPen (0.3 mg).

The main examples used are EpiPen Jr and EpiPen, which is also distributed under other trade names; however, similar limitations apply to other auto-injectors. In addition to the issue highlighted in Table II, manufacturer/distributor recommendations for weight-appropriate and age-appropriate use of auto-injectors containing 0.15 mg and 0.3 mg epinephrine differ in different countries—eg, in some countries, an auto-injector containing 0.15 mg is recommended only for individuals weighing ≤15 kg, and in other countries, an auto-injector containing 0.15 mg epinephrine is recommended only for individuals weighing 15 to 30 kg.<sup>12,21</sup>

auto-injectors and the need for additional fixed doses (0.05 mg, 0.1 mg, 0.2 mg, and 0.25 mg).<sup>12,21</sup> It is impossible to give a precise epinephrine dose of 0.01 mg/kg to a child weighing <15 kg by using EpiPen Jr (0.15 mg), and to a child weighing between 15 and 30 kg by using either the EpiPen Jr (0.15 mg) or the EpiPen (0.3 mg). Physicians must therefore choose whether to underdose such children with the EpiPen Jr or to overdose them with the EpiPen (Table II).

In a geographically defined population, using an administrative claims database, both EpiPen Jr (0.15 mg) and EpiPen (0.3 mg) auto-injectors were found to be dispensed (for anaphylaxis from all triggers) over nearly the entire pediatric age range: EpiPen Jr from 2 months to 16 years, 10 months; and EpiPen from 1 year, 8 months, to 16 years, 11 months.<sup>22</sup> The age of transition from EpiPen Jr to EpiPen ranged from 1 year, 10 months, to 16 years, 11 months, with a mean of 6 years, 6 months, at which time fewer than 3% of children weigh 30 kg and would receive an optimal dose of 0.01 mg/kg from an EpiPen.<sup>22</sup>

In a randomized, double-blind, parallel group study, children age 5 to 8 years and weighing 16 to 30 kg self-injected epinephrine by using either an EpiPen Jr or an EpiPen with the aid of a physician.<sup>13</sup> Children who received a dose of 0.01 to 0.014 mg/kg from an EpiPen had a significantly higher mean systolic blood pressure 30 minutes after injection; however, in every child, this was accompanied by pallor, tremor, anxiety, and palpitations. Some children also developed headache and nausea, and 1 child had an increase in the QTc interval. In contrast, children who received 0.008 to 0.009 mg/kg from an EpiPen Jr did not achieve a significant increase in blood

**TABLE III.** Case study: For a child weighing 22.5 kg, which auto-injector is best—EpiPen Jr (0.15 mg) or EpiPen (0.3 mg)?

In a child weighing 22.5 kg, the average weight for a 7-year-old, the EpiPen Jr delivers a 1.5-fold underdose and the EpiPen delivers a 1.3-fold overdose.

The decision to use EpiPen rather than EpiPen Jr may be guided by the presence of 1 or more of the following:

- Concurrent diagnosis of asthma
- Peanut, tree nut, milk, egg, fish or seafood anaphylaxis
- Poor access to emergency medical services, eg, living or vacationing in a remote rural area
- Dysfunctional/chaotic family situation
- No reliable transportation available
- History of previous life-threatening reaction (note, however, that *absence* of a history of life-threatening reaction does not eliminate the possibility of such a reaction in the future<sup>29,33,34</sup>)

See also footnote to Table II.

pressure and had fewer, milder, and more transient adverse effects limited to pallor, tremor, or anxiety.<sup>13</sup>

Until additional fixed doses of epinephrine are available in auto-injector formulations, physicians should carefully weigh the benefits versus the risks of the two available doses, 0.15 mg versus 0.3 mg, for each child (Table III). Lack of appropriate dose options should not deter them from recommending epinephrine for the first-aid, out-of-hospital treatment of anaphylaxis.

Some adolescents and adults may not be optimally treated with the maximum epinephrine dose of 0.3 mg available in an auto-injector. In addition, the 14.29 mm length needle on currently available auto-injectors may be

**TABLE IV.** Oral H<sub>1</sub>-antihistamines have a slow onset of action

|                   | Healthy, fasting young adults, single dose* |                                 | Healthy, fasting children, single dose* |                                 |
|-------------------|---------------------------------------------|---------------------------------|-----------------------------------------|---------------------------------|
|                   | t <sub>max</sub> (h)                        | Onset of activity (h postdose)† | t <sub>max</sub> (h)                    | Onset of activity (h postdose)† |
| First-generation  |                                             |                                 |                                         |                                 |
| Chlorpheniramine  | 2.8 ± 0.8                                   | 1                               | 2.5 ± 1.5                               | 1                               |
| Diphenhydramine   | 1.7 ± 1.0                                   | 1                               | 1.3 ± 0.5                               | 1                               |
| Hydroxyzine       | 2.1 ± 0.4                                   | 1                               | 2.0 ± 0.9                               | NA                              |
| Second-generation |                                             |                                 |                                         |                                 |
| Cetirizine        | 1.0 ± 0.5                                   | 0.7                             | 1.1 ± 0.8                               | 0.7-1                           |
| Desloratadine     | 1-3                                         | NA                              | NA                                      | NA                              |
| Fexofenadine      | 2.6                                         | 2                               | 2.4 ± 0.2                               | 1                               |
| Loratadine        | 1.2 ± 0.3                                   | 3                               | 1                                       | 1-2                             |

\*H<sub>1</sub>-antihistamine tablets used in most studies; liquid formulation of cetirizine, chlorpheniramine, diphenhydramine, hydroxyzine, and loratadine was given to fasting children.

†The time stated is the first interval after the dose at which symptoms and/or histamine-induced wheal or flare were significantly decreased compared with baseline in clinical pharmacology studies.<sup>32</sup>

NA, No published information.

too short to ensure intramuscular injection of epinephrine in obese individuals.<sup>23</sup>

### Epinephrine is widely dispensed, but not widely used in anaphylaxis

Epinephrine is widely dispensed in the community<sup>24</sup>; however, in retrospective studies of individuals dying from anaphylaxis, it has been consistently reported to be underused, and failure to inject it at all, delayed use, inappropriate dose, or inappropriate route of administration have been identified as contributing factors to death.<sup>25-28</sup> In 1 autopsy series, although epinephrine was given in 62% of fatal anaphylactic reactions triggered by a variety of agents, it was given before respiratory arrest in only 14% of these reactions.<sup>25</sup> In a study of 32 individuals dying from peanut or tree nut allergy, 12 did not receive epinephrine at all, 10 received it too late, 4 died despite receiving it in a timely manner, and for 6, no information was available.<sup>28</sup> In studies of individuals surviving anaphylaxis episodes, it has been reported that only 30% to 40% of subjects who required epinephrine actually received it.<sup>3,29</sup>

### Alternative routes of epinephrine administration in anaphylaxis

Many individuals with anaphylaxis and many caregivers of children with anaphylaxis are reluctant to inject epinephrine because of anxiety about using a needle. Administration of epinephrine through chlorofluorocarbon-containing pressurized metered-dose inhalers, in countries where these are still approved for use, contributes to relief of respiratory symptoms but is impractical for the treatment of other systemic effects, which requires 20 to 30 inhalations over a period of 4 minutes in an adult.<sup>17</sup> Oral epinephrine administration is ineffective because of metabolism by catechol-O-methyltransferase in the wall of the gastrointestinal tract and by monoamine oxidase in the wall of the gastrointestinal tract and in the liver.<sup>10</sup> Based on the precedent of using sublingual nitroglycerin for treatment of angina, the feasibility of sublingual epinephrine administration for the

first-aid treatment of anaphylaxis is being explored in clinical pharmacology studies.<sup>30</sup>

### OTHER APPROACHES TO THE FIRST-AID TREATMENT OF ANAPHYLAXIS

#### Supportive treatment

Individuals with anaphylaxis, especially those who feel faint or dizzy because of impending shock, should be kept in the supine position unless they are vomiting or experiencing severe respiratory distress. During extreme vasodilation, blood return to the vena cava, right and left chambers of the heart, and coronary arteries is more likely to be maintained if they are supine than if they are seated or standing.<sup>31</sup>

#### The epinephrine injection versus oral H<sub>1</sub>-antihistamine controversy

Histamine is an important mediator in anaphylaxis. H<sub>1</sub>-antihistamines are commonly used to relieve cutaneous signs and symptoms such as itching, flushing, and urticaria, but play little, if any, role in relief of bronchospasm or gastrointestinal symptoms; fail to relieve upper airway edema or hypotension; and, in usual doses, do not reduce the explosive release of histamine and other mediators of inflammation from mast cells and basophils. In clinical pharmacology studies conducted in fasting individuals, onset of activity of orally ingested H<sub>1</sub>-antihistamines does not occur until 40 to 60 minutes after ingestion (Table IV), and maximal activity is not achieved for at least 4 hours.<sup>32</sup>

In anaphylaxis, there are no prospective, randomized, double-blind, placebo-controlled clinical trials of oral H<sub>1</sub>-antihistamines or the algorithms for their use. In advance, there is no way to identify individuals whose anaphylaxis manifestations will be limited to the skin and for whom an H<sub>1</sub>-antihistamine will suffice. The course of an anaphylaxis episode and the window of opportunity for successful epinephrine treatment cannot be predicted with certainty and may differ from one person to another, and from one episode to another in the same person. In 3

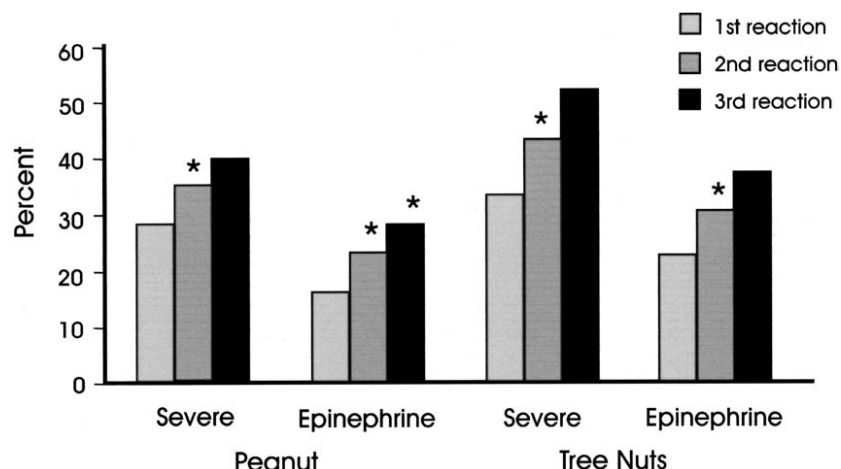


**FIG 5.** Mild anaphylactic reactions do not always remain mild. Individuals in the Food Allergy and Anaphylaxis Network's voluntary registry, or caregivers of children in the registry, answered a structured questionnaire about allergic reactions to peanut and tree nut. In comparison with initial reactions, a higher proportion of subsequent reactions were severe and were treated with epinephrine (first reaction vs third reaction,  $P < .001$ ; the asterisks indicate a reaction more severe than the previous reaction).<sup>33</sup>

different cohorts, adverse reactions to peanut and tree nut became more severe with time in 1/3 or more of individuals<sup>29,33,34</sup> (Fig 5).

The detailed algorithms developed to help physicians decide whether to give epinephrine or an H<sub>1</sub>-antihistamine in anaphylaxis<sup>6</sup> are useful in health care settings; however, in the first-aid treatment of anaphylaxis in the community, placing the burden of decision making ("if you observe this, do that") on individuals without medical training or resuscitation team backup may not be appropriate. Judgment may be clouded by central nervous system symptoms, fear, panic, or denial ("This can't possibly be happening again!"). Especially if very young or very ill, individuals may have difficulty verbalizing or describing their symptoms. Moreover, it may be difficult to assess clinical signs accurately in crowded, noisy, poorly lighted public places such as restaurants or airplanes where anaphylaxis to food occurs. In out-of-hospital settings, the inherent danger in the "try an antihistamine" approach or the "wait and see whether epinephrine is needed" approach relates to the observation that the median time to respiratory or cardiac arrest in individuals with anaphylaxis from food is 30 minutes.<sup>25</sup>

### Is there a role for activated charcoal in the first-aid treatment of anaphylaxis?

Activated charcoal, which is given in emergency departments (usually by nasogastric tube) for gastrointestinal decontamination after poisoning, has been suggested as a useful adjunct to the treatment of individuals with anaphylaxis to peanut, based on an *in vitro* study in which it rapidly adsorbed peanut protein in a dose-dependent manner at pH 3.5 or 7.4.<sup>35</sup> *In vitro* studies of adsorption of other foods and prospective studies of food adsorption in humans have not yet been conducted. Administration of activated charcoal may present a practical problem in the

first-aid treatment of food-induced anaphylaxis. Time is of the essence, and it would need to be given immediately after ingestion of the offending food; however, it may be difficult to administer by mouth in an adequate dose, because it clumps during storage, is messy, and is often vomited. Even for poisoning, it is not recommended for routine administration in nonmedical settings because of limited published experience with it in such settings.<sup>36</sup> In the first-aid treatment of anaphylaxis, an additional concern is that administration of activated charcoal may delay epinephrine injection.

### After first-aid treatment with epinephrine

After first-aid treatment with epinephrine injection, individuals should be transported to the nearest hospital emergency department for monitoring over a period of 4 to 6 hours. Additional doses of epinephrine, as well as oxygen, intravenous fluids, glucocorticoids, H<sub>1</sub>-antihistamines, H<sub>2</sub>-antihistamines, vasopressors, and other interventions, may be required.<sup>6</sup>

All individuals who have had anaphylaxis from food are at risk of subsequent reactions and therefore require follow-up. Ideally, this should include evaluation or re-evaluation by a board-certified allergist regarding the food trigger for the episode, recommendations for appropriate food avoidance measures and Medic Alert (Medic Alert Foundation International, Turlock, Calif) or other identification, coaching in the appropriate use of an epinephrine auto-injector, and development or review of an anaphylaxis emergency action plan.<sup>4-6</sup> The essentials of the emergency action plan include photograph identification of the person at risk and a list of their specific food triggers. If there is a concurrent diagnosis of asthma, which increases the risk of death from anaphylaxis,<sup>26-28</sup> this should be stated. The emergency action plan should also include a short list of anaphylaxis symptoms and

signs, pictorial instructions regarding prompt first-aid use of an epinephrine auto-injector, information about contacting the rescue squad and the family after epinephrine injection, and a reminder to transport the individual to an emergency department after first-aid treatment.

In the future, preventive treatment—for example, by injecting anti-IgE antibody at regular intervals—may be available to reduce the risk and severity of food-induced anaphylaxis.<sup>37</sup>

In summary, fatalities from anaphylaxis to food are, fortunately, uncommon; however, 90% of these deaths are preventable, and all who are involved in the care of individuals with food-triggered anaphylaxis share the responsibility for their prevention and first-aid treatment in the community.

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## Update

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Volume 113, Issue 6, June 2004, Page 1039

DOI: <https://doi.org/10.1016/j.jaci.2004.05.032>

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## Correction

With regard to the May 2004 article entitled "First-aid treatment of anaphylaxis to food: Focus on epinephrine" (2004;113:837-44): A serious dosage error appears in the section entitled "Epinephrine in the first-aid treatment of anaphylaxis." On page 837, in the fifth line of the subsection entitled "Evidence base for epinephrine use in anaphylaxis," the epinephrine dosage for children appears incorrectly as "a maximum of 0.3 mg/kg." **The correct maximum initial dose is 0.2 mg to 0.5 mg in adults; 0.01 mg/kg to a maximum of 0.3 mg in children.** The sentence should read as follows:

Recommendations for epinephrine dosing in the first-aid, out-of-hospital treatment of anaphylaxis are based on anecdotal experience and may vary with regard to maximum initial dose (0.2 mg to 0.5 mg in adults; 0.01 mg/kg to a maximum of 0.3 mg in children), route of injection (subcutaneous vs. intramuscular), and interval between doses (5-30 minutes).<sup>6-9</sup>

The incorrect dosage was a major error on the part of the publisher. If implemented, the incorrect dosage could result in a fatal epinephrine overdose for a child.