EpiPen Jr versus EpiPen in young children weighing 15 to 30 kg at risk for anaphylaxis

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Background: The EpiPen Jr (0.15 mg) and EpiPen (0.3 mg) auto-injectors, widely prescribed for the out-of-hospital treatment of anaphylaxis, have not been compared prospectively in young children.
Objective: The purpose of this investigation was to study the rate and extent of epinephrine absorption after use of the EpiPen Jr and the EpiPen in children weighing 15 to 30 kg.
Methods: In a randomized, double-blinded, parallel-group pilot study, children at risk for anaphylaxis self-injected epinephrine using either an EpiPen Jr or an EpiPen with the aid of a physician. Plasma epinephrine concentrations, blood glucose, blood pressure, heart rate, and adverse effects were monitored before and for 180 minutes after the injection.
Results: Children (age [mean ± SEM], 5.4 ± 0.4 years; weight [mean ± SEM], 18.0 ± 0.6 kg) who injected epinephrine with an EpiPen Jr achieved a maximum plasma concentration (mean ± SEM) of 2037 ± 541 pg/mL at 16 ± 3 minutes. Children (6.6 ± 0.5 years; 25.4 ± 1.5 kg) who injected epinephrine with an EpiPen achieved a maximum plasma concentration of 2289 ± 405 pg/mL at 15 ± 3 minutes. Mean systolic blood pressure 30 minutes after epinephrine injection was significantly higher with the EpiPen than with the EpiPen Jr. After injection with the EpiPen Jr, every child experienced transient pallor; some also experienced tremor and anxiety. After injection with the EpiPen, every child developed transient pallor, tremor, anxiety, and palpitations or other cardiovascular effects; some also developed headache and nausea.
Conclusion: Epinephrine injection with the EpiPen rather than the EpiPen Jr raised the systolic blood pressure significantly but also caused more adverse effects. The beneficial pharmacologic effects and the adverse pharmacologic effects of epinephrine cannot be dissociated. For the out-of-hospital treatment of anaphylaxis, additional premeasured, fixed doses of epinephrine would facilitate more precise dosing in young children. (J Allergy Clin Immunol 2002;109:171-5.)

Key words: *Epinephrine, adrenaline, intramuscular injection, children, systemic anaphylaxis, severe acute allergic reaction, food allergy, Hymenoptera venom allergy, latex allergy*

Abbreviations used
C_{max}: Maximum concentration
t_{max}: Time of maximum concentration

Prompt injection of epinephrine in a dose of 0.01 mg/kg intramuscularly is life-saving in the treatment of systemic anaphylaxis (severe acute allergic reaction).[1-9] For out-of-hospital treatment of young children with anaphylaxis, the user-friendly EpiPen Jr and EpiPen auto-injectors,[10,11] each of which provides a sterile, premeasured epinephrine dose, are commonly recommended. The EpiPen Jr contains epinephrine 0.15 mg, which is an optimal dose for patients weighing approximately 15 kg; the EpiPen contains epinephrine 0.3 mg, which is optimal for patients weighing approximately 30 kg or more.

Both auto-injectors, the EpiPen Jr and the EpiPen, are dispensed over almost the entire age range of the pediatric population from birth to adolescence, suggesting that potential overdosing and potential underdosing might occur.[12,13] The mean age of transition from having the EpiPen Jr dispensed to having the EpiPen dispensed has been reported as 6 years 6 months ± 2 years 8 months (range, 1 year 10 months to 16 years 11 months).[12]

Some physicians are not even aware that the EpiPen Jr, as distinct from the EpiPen, is available.[14] Those who know of the existence of both the EpiPen Jr and the EpiPen face a dilemma: which dose of epinephrine, 0.15 mg or 0.3 mg, should be selected if neither dose is optimal for a young child? Little guidance is found in reference textbooks[1-6] and consensus statements from expert groups[7] with regard to this issue, though one group has recommended that the EpiPen Jr should be used for children weighing 10 to 20 kg and the EpiPen should be used for children weighing more than 20 kg[8]; another group has recommended that the EpiPen should be used for children weighing more than 25 kg.[9] Information available from distributors of the auto-injectors in national compendia and package inserts changes over time, differs in different countries, and is potentially confusing. The *Physicians' Desk Reference*, an internationally used compendial resource, currently provides the following advice:

> For pediatric use, the appropriate dosage may be 0.15 or 0.3 mg depending upon the body weight of the patient. A dosage of 0.01 mg/kg body weight is recommended. The EpiPen Jr, which provides a dosage of 0.15 mg, may be more

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Supported by the Children's Hospital Foundation of Manitoba, Inc. No financial or in-kind support was provided for this study by any corporate sponsor.
Received for publication August 24, 2001; revised September 27, 2001; accepted for publication October 3, 2001.
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0091-6749/2002 $35.00 + 0 **1/87/120758**
doi:10.1067/mai.2002.120758

> appropriate for patients weighing less than 30 kg. However, the prescribing physician has the option of prescribing more or less than these amounts.[10]

In some countries, though, the instructions on the EpiPen Jr itself and the package insert for the EpiPen Jr currently state that it should be used "for patients weighing 15 kg and less only"![11]

To address this dilemma, we performed a pilot study of the relative rate and extent of epinephrine absorption after injection from the EpiPen Jr and after injection from the EpiPen in allergic children age 4 to 8 years old who were at risk for anaphylaxis. We hypothesized that both the EpiPen Jr 0.15 mg auto-injector and the EpiPen 0.3 mg auto-injector would result in significant increases in plasma epinephrine concentrations and significant systemic effects in this population. We tested this hypothesis in a prospective, randomized, double-blinded, parallel-group pilot study.

METHODS

The study was approved by the University of Manitoba Research Ethics Board. Assent for participation was obtained from each child; written, informed consent for each child's participation was obtained from his or her parents.

Selection of participants

The children were recruited from the practices of pediatric allergists at the Health Sciences Centre Children's Hospital. A child was eligible to participate if he or she (1) was 4 to 8 years of age, (2) weighed 15 to 30 kg, (3) had a history of severe acute allergic reactions, and (4) carried an EpiPen Jr or EpiPen, as prescribed by his or her personal physician for self-injection in the event of a subsequent reaction. A child was excluded from participation if he or she (1) had participated in a previous epinephrine study, (2) did not assent to the monitoring procedures, venipuncture, or epinephrine injection, (3) had a history of a recent acute illness, (4) had any chronic illness other than asthma, allergic rhinitis, or atopic dermatitis, (5) had required any oral or injected medication during the preceding month, and (6) could not discontinue inhaled β_2-adrenergic agents, such as albuterol (Ventolin) for asthma, or any topical α-adrenergic medication being used for allergic rhinoconjunctivitis either for 24 hours before or during the visit in which the epinephrine injection was administered.

Study outline

During visit 1, an introduction to the study was given and the children were assessed with regard to their ability to meet the inclusion and exclusion criteria; they and their parents were then given the opportunity to discuss the monitoring procedures and the epinephrine injection. Each child's personal physician was advised about his or her participation in the study.

On visit 2, the child arrived at the John Buhler Research Centre Allergy Laboratory at 11:30 AM and was studied individually in a quiet room with a parent present. The child abstained from use of any medication and from ingestion of any methylxanthine-containing dietary item—eg, chocolate, cocoa, and cola—both for 24 hours before and during the visit. An indwelling venous catheter was inserted 1 to 1.5 hours after application of EMLA (eutectic mixture of local anesthetic) cream (Astra Pharma Inc, Mississauga, Ontaio, Canada) to the site of venipuncture. Systolic and diastolic blood pressures were measured at 3 consecutive 5-minute intervals. An electrocardiogram was obtained, and monitoring of blood pressure and of heart rate and rhythm was begun (Dinamap Vital Signs Monitor, Critikon, Inc, Johnson & Johnson, Tampa, Fla, and Cardiograph PageWriter XLi [M1700A], Hewlett-Packard Company, McMinnville, Ore, respectively).

Each of the children was randomly assigned to receive a single intramuscular injection of epinephrine from either the EpiPen Jr (0.15 mg) or the EpiPen (0.3 mg). The EpiPen Jr and EpiPen auto-injectors (lot numbers 0C5066 and 0C6301, respectively) used in the study had been purchased from a local pharmacy and third-party–blinded at another site by encasing the auto-injector barrel with opaque black tape.

Before the epinephrine injection, optimal use of EpiPen Jr and EpiPen auto-injectors was reviewed in detail with the children and their parents. The child then self-injected the EpiPen Jr or EpiPen with the aid of a physician, listened for the "click," and observed the stopwatch while counting out the 10-second interval between the injection and the withdrawal of the EpiPen from the site. Each injection was made at the midpoint of the vastus lateralis muscle of the thigh opposite the arm in which the indwelling catheter was inserted.

Before injection and at 5, 10, 15, 20, 30, 45, 60, 75, 90, 105, 120, 150, and 180 minutes afterward, 3.5-mL blood samples for plasma epinephrine measurement were obtained from the indwelling venous catheter. Immediately after each blood sample was obtained, the blood glucose concentration in it was measured through use of an Elite glucometer (Bayer Inc, Health Care Division, Etobicoke, Ontario, Canada). Before injection and at 30, 60, 120, and 180 minutes afterward, systolic and diastolic blood pressures and heart rate were recorded and a rhythm strip was obtained. The child rested supine on a bed for 5 minutes before these measurements were made. At the time of blood sampling, any adverse effects observed or reported in response to direct questioning were recorded on the case record form. A lunch brought from home was eaten 35 to 40 minutes after epinephrine injection.

Measurement of plasma epinephrine concentrations

Blood samples were centrifuged at 4°C. Plasma was transferred into an appropriately labeled polypropylene tube with screw cap, frozen promptly in an upright position, and stored at –20°C until analysis.

After the plasma was thawed, solid/liquid-phase extraction was performed; the efficiency was 75% to 80%. Epinephrine concentrations were measured by using a high performance liquid chromatography reverse-phase system (Waters Corp., Milford, Mass) with electrochemical detection. With modification of this assay, which measures both endogenous and exogenous epinephrine, it was possible to detect as little as 5 pg/mL (0.025 nmol/L per mL) of epinephrine. Calibration curves were linear over the range 25 to 1000 pg (0.125-5 nmol) with a coefficient of variation of 3% at 1000 pg and 10% at 25 pg.[15]

Plasma epinephrine concentration–versus-time plots were made, and pharmacokinetic parameters such as maximum concentration (C_{max}) and time of maximum concentration (t_{max}) were calculated through use of standard equations and the computer program PCNONLIN (Scientific Consulting, Apex, NC). Blood pressure and heart rate–versus–plasma epinephrine concentrations were evaluated over time through use of PCSAS computer programs, ANOVA, analysis of covariance, and linear regression analysis. Differences were considered to be significant at $P < .05$.[16]

RESULTS

A total of 153 families, each with a child aged 4 to 8 years who was at risk for anaphylaxis and for whom the

TABLE I. Children receiving epinephrine injection: demographic data

	Children using EpiPen Jr (0.15 mg)	Children using EpiPen (0.3 mg)
No. of children in group (boys)	5 (3)	5 (3)
Age (y): mean ± SEM (range)	5.4 ± 0.4 (5-7)	6.6 ± 0.5 (5-8)
Weight (kg): mean ± SEM (range)	18.0 ± 0.6 (16-20.4)*	25.4 ± 1.5 (21.5-30)*
Dose (mg/kg)	0.008-0.009	0.010-0.014
History of anaphylaxis to peanut	4	4
History of anaphylaxis to egg	1	0
History of anaphylaxis to fish	0	1
Epinephrine formulation carried by child, as prescribed by personal physician		
EpiPen Jr (0.15 mg)	3	1
EpiPen (0 .3 mg)	2	4

*$P < .05$.

TABLE II. Adverse effects after epinephrine injection

	Children receiving EpiPen Jr (0.15 mg)	Children receiving EpiPen (0.3 mg)
Pallor	5	5
Tremor	3	5
Anxiety*	2	5
Cardiovascular†	0	5
Headache	0	2
Nausea	0	2

*After injection, the children spontaneously described themselves as feeling "scared," "frightened," or "weird"; one child was irritable, and another child was tearful.
†Palpitations were described by 3 children, who used the terms "heart pounding," "heart beating fast," and "feeling a thump at the sides of my forehead"; prolonged vasoconstriction leading to difficulty in obtaining blood samples from the indwelling venous catheter occurred in a fourth child, and the QTc interval was prolonged in a fifth child (see text for details).

EpiPen Jr or the EpiPen had been prescribed by his or her personal physician, were telephoned with regard to involvement in this study. Twelve families agreed to participate. Most of the families who were contacted declined because they did not want their children to have an epinephrine injection or a "needle." Some parents commented that their children would never need the EpiPen Jr or EpiPen that had been prescribed because the provoking factor for the previous severe acute allergic reaction was being strictly avoided.

Twelve children completed visit 1. During visit 2, a girl aged 5 years and a boy aged 6 years became tearful during venipuncture for intravenous catheter insertion, appeared to withdraw their assent to participate in the study, and were therefore not given epinephrine injections. The 10 children who received epinephrine (5 from the EpiPen Jr and 5 from the EpiPen) and completed visit 2 are described in Table I. The 5 children who used the EpiPen Jr (epinephrine dose, 0.008-0.009 mg/kg) had a mean ± SEM age of 5.4 ± 0.4 years, a mean ± SEM weight of 18.0 ± 0.6 kg, and a mean ± SEM maximum plasma epinephrine concentration of 2037 ± 541 pg/mL. The 5 children who used the EpiPen (epinephrine dose, 0.01-0.014 mg/kg) were aged 6.6 ± 0.5 years, weighed 25.4 ± 1.5 kg, and had a maximum plasma epinephrine concentration of 2289 ± 405 pg/mL. After use of the EpiPen Jr, maximum plasma epinephrine concentrations were achieved within 16 ± 3 minutes; after use of the EpiPen, they were achieved within 15 ± 3 minutes (Fig 1). Systolic and diastolic blood pressure and heart rate values are shown in Fig 2, *A* and *B*, respectively. All of the children had normal, stable blood pressure and heart rate measurements at baseline. At 30 minutes after injection, the mean systolic blood pressure was significantly higher in the children who received epinephrine from the EpiPen than in those who received it from the EpiPen Jr. In addition, at 105 and 150 minutes after injection, the mean blood glucose concentrations were significantly higher in those who received epinephrine from the EpiPen than in those who received it from the EpiPen Jr.

Some children commented on the brief loud noise heard when the epinephrine injection was being given from the EpiPen Jr or the EpiPen. One child complained of pain lasting for 5 to 10 minutes at the injection site. All children experienced one or more transient adverse effects after epinephrine injection (Table II). Pallor was universal. After injection of epinephrine 0.15 mg from an EpiPen Jr, pallor lasted only 5 minutes; it was accompanied by tremor in 3 children and by anxiety in 2 children. After injection of epinephrine 0.3 mg from an EpiPen, all children developed pallor, tremor, and anxiety; other adverse effects, including palpitations, headache, and nausea, also occurred. A child with a weight of 21.5 kg who used the EpiPen (0.3 mg epinephrine) had profound pallor, tremor, anxiety, headache, and nausea for 10 minutes after the injection. This child also developed marked

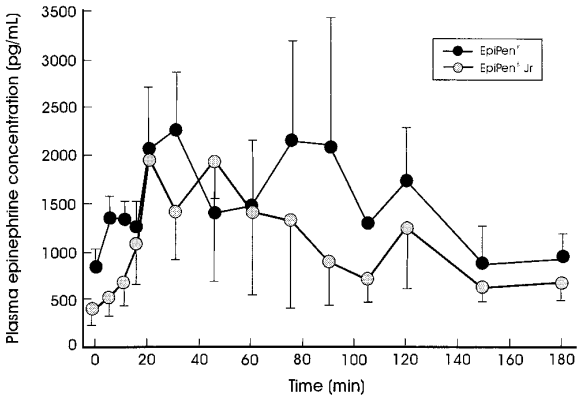

FIG 1. Mean ± SEM plasma epinephrine concentrations versus time after injection into the thigh of either epinephrine 0.15 mg (EpiPen Jr) or epinephrine 0.3 mg (EpiPen).

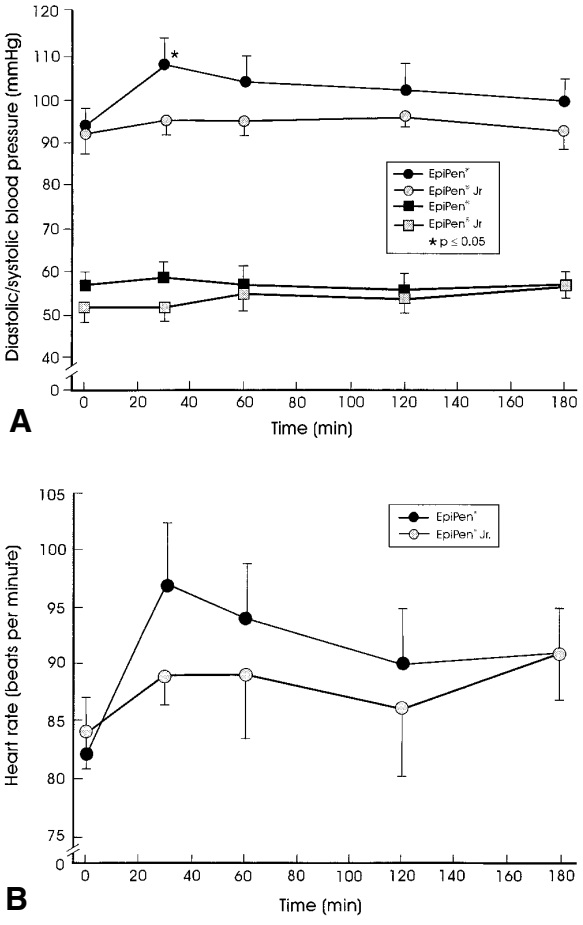

FIG 2. A, Mean ± SEM systolic and diastolic blood pressures after epinephrine injection. **B,** Mean ± SEM heart rate after epinephrine injection.

vasoconstriction that lasted for 105 minutes after injection, as evidenced by difficulty in obtaining blood samples from the indwelling catheter; there were no adverse effects from 105 to 180 minutes after epinephrine injection. Another child, with a weight of 30 kg, who used the EpiPen (0.3 mg epinephrine) had pallor, tremor, and anxiety lasting 10 minutes after the injection; this child also developed prolongation of the QTc interval lasting 120 minutes after injection (QTc pre-epinephrine, 410 msec; peak QTc post-epinephrine, 449 msec). At no time during the study did this child experience palpitations, dizziness, or syncope. When subsequently evaluated by a pediatric cardiologist, he was found to have a normal heart with no evidence of long QT syndrome.

DISCUSSION

This study was performed in a practical attempt to address the dilemma faced by physicians involved in the care of young children at risk for anaphylaxis outside a hospital setting: how to decide which of the 2 available fixed doses of epinephrine (either 0.15 mg from an EpiPen Jr or 0.3 mg from an EpiPen) to prescribe for a young child weighing between 15 and 30 kg for whom neither dose would be optimal. We have shown that epinephrine injected either from an EpiPen Jr (0.15 mg) or an EpiPen (0.3 mg) leads to prompt achievement of peak plasma epinephrine concentrations. Failure to identify a significant difference in peak concentration after the 2 different doses was likely due to the small sample size and the fact that despite randomization, the children receiving epinephrine from the EpiPen Jr were significantly smaller than those receiving it from the EpiPen. We have also shown that (1) peak pharmacologic effects were achieved promptly after use of the EpiPen Jr and the EpiPen and (2) in comparison with injection of epinephrine 0.15 mg from the EpiPen Jr, injection of epinephrine 0.3 mg from the EpiPen produced a significant increase in systolic blood pressure that was accompanied by more and longer-lasting adverse effects.

In prescribing an EpiPen Jr (0.15 mg) or an EpiPen (0.3 mg) for a child weighing 15 to 30 kg, the physician is required to exercise considerable clinical judgment. Prescription of an EpiPen Jr (0.15 mg) might be influenced by one or more of the following factors: weight close to 15 kg; no history of asthma (a known poor prognostic factor in anaphylaxis); history of mild anaphylaxis, for example, limited to hives and wheezing; ready access to an emergency department at all times. In this regard, it is important to note that a history of a mild episode of anaphylaxis on 1 occasion is not necessarily a reliable predictor of a mild reaction on subsequent occasions, at least for reactions triggered by peanut.[17,18] In contrast, prescription of an EpiPen (0.3 mg) might be influenced by one or more of the following factors: weight close to 30 kg; concurrent asthma; history of a severe episode of anaphylaxis, including respiratory distress and hypotension; poor emergency department access (as in the case of a family lacking readily available transportation or living or vacationing in a remote rural area).

In an earlier prospective, randomized, blinded investigation of allergic children aged 7 to 11 years and weighing 19 to 39 kg—age/weight specifications that overlap

those of the children in the present study—epinephrine injected from the EpiPen (0.3 mg) by an experienced allergy nurse resulted in a C_{max} of 2136 ± 351 pg/mL; the t_{max} was 8 ± 2 minutes. In the present study, though the C_{max} epinephrine after use of the EpiPen (0.3 mg) was similar to that reported previously, the t_{max} was later, possibly because the children self-injected the epinephrine less forcefully than the nurse had done in the previous study. These data suggest that though a child 5 to 8 years old is capable of self-injecting epinephrine using an EpiPen Jr or an EpiPen, it is preferable that an adult actually give the injection.

The life-saving benefits of prompt epinephrine injection in anaphylaxis—ideally *before* respiratory distress, stridor, wheezing, or hypotension occur—outweigh the risk of pharmacologic adverse effects. The adverse effects of epinephrine, including pallor, tremor, anxiety, palpitations, headache, and nausea are true pharmacologic effects,[19] which occur regardless of the route of epinephrine administration[20-24] and might be unavoidable in some patients because of the narrow toxic-therapeutic ratio of the drug.[20-25] They are also dose-related, and in this study they were more frequent and more severe in the children receiving epinephrine 0.010 to 0.014 mg/kg than in those receiving epinephrine 0.008 to 0.009 mg/kg. They are definitely *not* a reason to delay or avoid epinephrine injection.

For young children with anaphylaxis requiring out-of-hospital first-aid treatment, there currently are few options. The Ana-Kit is no longer available.[10] Most parents have difficulty in drawing up an epinephrine dose rapidly and accurately from an ampule.[26] Additional user-friendly, premeasured, fixed-doses of epinephrine are therefore needed to facilitate more precise dosing on a milligrams-per-kilogram basis in young children.

We are grateful to the children who participated in this study and to their parents. We thank Ms Lana M. Johnston, RN, for excellent professional assistance and Janet R. Roberts, MD, FRCPC, Wade T. A. Watson, MD, FRCPC, and Allan B. Becker, MD, FRCPC, for allowing us to study their patients.

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