

Can Epinephrine Inhalations Be Substituted for Epinephrine Injection in Children at Risk for Systemic Anaphylaxis?

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ABSTRACT. *Background.* For out-of-hospital treatment of anaphylaxis, inhalation of epinephrine from a pressurized metered-dose inhaler is sometimes recommended as a noninvasive, user-friendly alternative to an epinephrine injection.

Objective. To determine the feasibility of administering an adequate epinephrine dose from a metered-dose inhaler in children at risk for anaphylaxis by assessing the rate and extent of epinephrine absorption after inhalation.

Methods. We performed a prospective, randomized, observer-blind, placebo-controlled, parallel-group study in 19 asymptomatic children with a history of anaphylaxis. Based on the child's weight, 10, 15, or 20 carefully supervised epinephrine or placebo inhalations were attempted. Before dosing, and at intervals from 5 to 180 minutes after dosing, we monitored plasma epinephrine concentrations, blood glucose, heart rate, blood pressure, and adverse effects.

Results. Eleven children (mean $\pm$ standard error of the mean: 9 ± 1 years and 33 ± 3 kg) in the epinephrine group were able to inhale 11 ± 2 (range: 3–20) puffs, equivalent to $74\% \pm 7\%$ of the precalculated dose or 0.078 ± 0.009 mg/kg. They achieved a mean peak plasma epinephrine concentration of 1822 ± 413 (range: 230–4518) pg/mL at 32.7 ± 6.2 minutes. Eight children (10 ± 1 years of age and 33 ± 5 kg) in the placebo group were able to inhale 12 ± 2 (range: 8–20) puffs, $89\% \pm 3\%$ of the precalculated dose, and had a peak endogenous plasma epinephrine concentration of 1316 ± 247 (range: 522–2687) pg/mL at 44.4 ± 16.7 minutes. In the children receiving epinephrine compared with those receiving placebo, mean plasma epinephrine concentrations were not significantly higher at any time, mean blood glucose concentrations were significantly higher from 10 to 30 minutes, mean heart rate was not significantly different at any time, and mean systolic and diastolic blood pressures were not significantly increased at most times. After the inhalations of epinephrine or placebo, the children complained of bad taste and many experienced cough or dizziness. After inhaling epinephrine, 1 child developed nausea, pallor, and muscle twitching.

Conclusions. Despite expert coaching, because of the number of epinephrine inhalations required and the bad taste of the inhalations, most children were unable to

inhale sufficient epinephrine to increase their plasma epinephrine concentrations promptly and significantly. Therefore, we urge caution in recommending epinephrine inhalation as a substitute for epinephrine injection for out-of-hospital treatment of anaphylaxis symptoms in children. *Pediatrics* 2000;106:1040–1044; epinephrine, adrenaline, anaphylaxis, severe acute allergic reaction, pressurized metered-dose inhaler, child, adolescent.

Systemic anaphylaxis frequently occurs outside of a hospital setting, where common triggers such as foods, latex rubber, insect stings and bites, and physical factors such as exercise or cold exposure may be inadvertently encountered by at-risk children and adolescents.^{1–4} Prompt, prehospital treatment is life-saving.⁵ Injection of epinephrine, preferably by the intramuscular route, is the treatment of first choice.^{5,6} When administered by this route, epinephrine is rapidly absorbed, and peak plasma concentrations and peak systemic effects occur promptly.⁶ Despite this, many children with a history of anaphylaxis do not carry injectable epinephrine^{1–4} and many children, caregivers, and even physicians do not know how to use injectable epinephrine appropriately.^{7–9} In addition, concerns are often expressed about some epinephrine autoinjectors with regard to high cost and the inability to administer more than one epinephrine dose, if the need should arise because of progressive or biphasic anaphylaxis symptoms.

For out-of-hospital treatment of anaphylaxis, inhalation of epinephrine from a metered-dose inhaler is recommended worldwide as a noninvasive, user friendly alternative to epinephrine injection.^{10–12} Inhalation leads to a high epinephrine concentration in the upper and lower airways, where obstruction often occurs during an anaphylaxis episode^{1,2} and where there is a large surface area for epinephrine absorption. Other advantages promulgated for inhalation include absence of pain from injection, low cost, nonprescription availability in many countries, potential for administration of multiple doses, ease of inhalation compared with injection, and freedom from adverse effects.^{10–12} In addition, schools and youth organizations are more accepting of inhalers than they are of needles.

We hypothesized that under expert supervision, children would be able to achieve a prompt, significant increase in plasma epinephrine concentrations by inhaling epinephrine from a pressurized metered-dose inhaler. We tested this hypothesis in a prospec-

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tive, randomized, observer-blind, parallel-group, placebo-controlled study in allergic children at risk for anaphylaxis.

METHODS

Before entry into this study, which was approved by the University of Manitoba Research Ethics Board, assent was obtained from each child, and written informed consent was obtained from a parent of each child.

Subject Selection

Children were eligible to participate if they were age 6 to 14 years old, had a history of severe allergies and systemic anaphylaxis, and carried injectable epinephrine with them at all times.

They were excluded if they: were obese, smoked, or had a history of an acute or chronic disorder other than anaphylaxis, asthma, allergic rhinitis, or atopic dermatitis; specifically, if they had a history of hypertension, cardiac disorder, recurrent headaches, seizures, or other central nervous system disorder. They were also excluded from participation if they did not assent to the epinephrine or placebo inhalations and the venipuncture, had a recent acute illness, required any oral or injected medication during the month before the study or during the study, or could not discontinue adrenergic agents such as albuterol (Ventolin, Glaxo Wellcome, Mississauga, Ontario, Canada) for 24 hours before or during the study. The only medications permitted on the study day were low-dose inhaled glucocorticoids for mild asthma and low-dose intranasal glucocorticoids for allergic rhinitis.

Study Outline

During a preliminary visit, children were assessed for their ability to meet the inclusion criteria and were given the opportunity to discuss the study, including the epinephrine or placebo inhalations, the venipuncture for intravenous catheter insertion and blood sampling, and the monitoring procedures.

On the study day, they arrived at the Health Sciences Clinical Research Center Pediatric Allergy Laboratory at ~1130 hours. They abstained from ingestion of methylxanthine-containing dietary items, eg, chocolate, cocoa, or cola for 24 hours before and during the study. An indwelling venous catheter was inserted after application of eutectic mixture of local anesthetics cream (Astra Pharma Inc, Mississauga, Ontario, Canada) to the site of venipuncture. Monitoring of systolic and diastolic blood pressure and heart rate and rhythm was begun (Dinamap Vital Signs Monitor, Critikon, Inc, Johnson & Johnson Company, Tampa, FL and Cardiograph PageWriter XLi [M1700A], Hewlett-Packard Company, McMinnville, OR, respectively).

Epinephrine Administration and Rationale for Selection of Epinephrine Dose

The children were studied one at a time to avoid inadvertent inhalation of aerosolized epinephrine by those in the placebo group. Inhalations took place in a room adjacent to the Allergy Laboratory, from which they were transported back and forth by wheelchair. An experienced pediatric nurse, who was not otherwise involved in the study, assessed each child's ability to use a pressurized metered-dose inhaler and provided appropriate coaching to facilitate optimal technique. Before each inhalation, the canister was shaken. The child exhaled and placed the mouthpiece between his or her lips, then released the dose while taking a slow, deep breath in, and breath-held for 5 to 10 seconds after completing the inhalation.

The children were randomized to receive either epinephrine (Bronkaid Mistometer, Sanofi Canada, Markham)¹³ or placebo (vehicle) by pressurized metered-dose inhaler. The Bronkaid Mistometer contains epinephrine United States Pharmacopeia 0.5% (5.5 mg/mL) and delivers ~0.25 mg epinephrine through the mouthpiece (0.275 mg through the valve) per inhalation.

The number of inhalations of epinephrine or placebo administered was based on the child's body weight. Selection of the epinephrine dose was extrapolated from studies in adults in which 10 to 30 epinephrine inhalations were administered to achieve a significant increase in plasma epinephrine concentrations.^{14–16} The time over which the inhalations were taken was measured using a stopwatch. Children weighing 20 to 30 kg were

asked to take 10 inhalations during a 2-minute period; those weighing 30 to 40 kg were asked to take 15 inhalations during a 3-minute period; and those weighing >40 kg were asked to take 20 inhalations during a 4-minute period. If a child was unable to take a full dose during the allotted time, the number of inhalations was recorded, the time elapsed between the first and last inhalations was recorded, and he or she remained in the study. The nurse coach recorded each child's comments, if any, about the inhalations, in addition to her own observations.

Outcome Measures

Before the inhalations, and at 5, 10, 15, 20, 30, 40, 60, 90, 120, and 180 minutes afterward, a 3.5-mL blood sample for plasma epinephrine and blood glucose measurement was obtained from the indwelling venous catheter. Before the inhalations and at 30, 60, 120, and 180 minutes afterward, heart rate and blood pressure were monitored and a rhythm strip was obtained. The child rested quietly for 5 minutes before each of these measurements were recorded. If heart rate and/or blood pressure were elevated at the end of the study, the child remained in the laboratory until they had returned to predose baseline values. At each time of blood sampling, any adverse effects observed or reported in response to direct questioning were recorded on the case record forms.

Immediately after each blood sample was obtained, the blood glucose concentration in it was measured using an Elite Glucometer (Bayer, Inc, Healthcare Division, Etobicoke, Ontario, Canada).

The remainder of each blood sample was 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 thawing the plasma, solid/liquid-phase extraction was performed, with an efficiency of 75% to 80%. Epinephrine concentrations were measured using a high-performance liquid chromatography reverse-phase system with electrochemical detection (Waters Corp, Milford, MA).¹⁷ With modification of this assay, it was possible to detect as little as 5 pg/mL (0.025 nM/mL) of epinephrine.⁶ Calibration curves were linear over the range 25 to 1000 pg (0.125–5 nM) with a coefficient of variation of 3% at 1000 picograms and 10% at 25 picograms.

Data Analysis

The rate and extent of epinephrine absorption were calculated from plasma epinephrine concentration versus time plots using standard pharmacokinetic equations and the computer program WinNonlin (Scientific Consulting, Apex, NC).

Blood pressure and heart rate versus plasma epinephrine concentrations were evaluated over time after epinephrine administration. Analysis of variance, analysis of covariance, and linear regression analyses were performed using PCSAS computer programs (SAS Institute Inc, Cary, NC). Differences were considered to be significant at $P < .05$.¹⁸

RESULTS

All 19 participants in this study had a history of systemic anaphylaxis and carried injectable epinephrine with them around-the-clock in case of inadvertent contact with the trigger factor to which they were sensitive and a subsequent severe allergic reaction. In the epinephrine group, 10/11 children had reacted to peanut or tree nut and 1 to an insect sting. In the placebo group, 6/8 had reacted to peanut or tree nut, 1 to fish, and 1 to an insect sting. The demographics of the 2 groups are shown in Table 1.

Most children (9/11 in the epinephrine group and 6/8 in the placebo group) also had a history of asthma and were accustomed to using a pressurized metered-dose inhaler for glucocorticoid and β_2 -adrenergic agonist treatment. Despite this, only 2/11 children in the epinephrine group and 2/8 in the placebo group were able to take 100% of the inhalations theoretically required to achieve a significant elevation in epinephrine concentrations. In the epinephrine group, the mean number of inhalations

TABLE 1. Epinephrine Versus Placebo Inhalations

Mean $\pm$ SEM (Range)	Epinephrine*	Placebo
No. of children in group	11 (10 male)	8 (5 male)
Age (y)	9 $\pm$ 1 (6–14)	10 $\pm$ 1 (6–14)
Weight (kg)	33 $\pm$ 3 (20–50)	33 $\pm$ 5 (21–62)
Height (cm)	136 $\pm$ 4 (117–153)	134 $\pm$ 8 (115–152)
Number of inhalations	11 $\pm$ 2 (3–20)	12 $\pm$ 2 (8–20)
Epinephrine dose (mg)	2.64 $\pm$.41 (.75–5.0)	—
Epinephrine dose (mg/kg)	0.078 $\pm$ 0.009 (0.050–0.127)	—
Dose (% amount prescribed)	74 $\pm$ 7 (30–100)	89 $\pm$ 3 (80–100)
C _{baseline} (pg/mL)	436 $\pm$ 106 (34–1281)	561 $\pm$ 192 (41–1481)
C _{max} (pg/mL)	1822 $\pm$ 413 (230–4518)	1316 $\pm$ 247 (522–2687)
t _{max} (min)	32.7 $\pm$ 6.2 (5–60)	44.4 $\pm$ 16.7 (5–120)
AUC (ng/mL/min)	200.8 $\pm$ 57.5 (86.7–568.5)	86.8 $\pm$ 14.7 (41.9–161.2)

AUC indicates area under the plasma concentration versus time curve ($t = 0$ –3 h); SEM, standard error of the mean; C_{max}, peak plasma epinephrine concentrations; t_{max}, time at which peak epinephrine concentrations were achieved.

* There was no significant difference between the treatment groups.

taken was 11 $\pm$ 2 (range: 3–20) puffs, 74% $\pm$ 7% of the precalculated dose, or 2.64 $\pm$ 0.41 mg (0.078 $\pm$ 0.009 mg/kg). In the placebo group, the mean number of inhalations taken was 12 $\pm$ 2 (range: 8–20) puffs, 89% $\pm$ 3% of the precalculated dose (Table 1).

The rate and extent of epinephrine absorption after inhalation and the endogenous epinephrine data after placebo inhalation are also presented in Table 1. Baseline plasma epinephrine concentrations were similar in the children in the epinephrine and placebo groups. Mean plasma epinephrine concentrations were higher from 20 to 180 minutes after epinephrine inhalations, compared with epinephrine concentrations after placebo inhalations. There were large variances at each time point after epinephrine inhalation, and the groups did not differ significantly at any time point ($P > .05$; Fig 1). Mean blood glucose concentrations were significantly higher ($P \leq .05$) from 10 to 30 minutes after the epinephrine inhalations, compared with the placebo inhalations. Mean heart rate and diastolic blood pressure did not differ significantly between the 2 groups at any time. Mean systolic blood pressures were significantly higher at baseline and at 30 minutes in the children inhaling epinephrine, compared with those inhaling placebo (Table 2).

Adverse effects were common. Ten of 11 children in the epinephrine group and 4/8 children in the placebo group complained about the taste of the

inhalations. Verbatim descriptions included: “bad,” “horrible,” “burning,” “awful,” “yucky,” “ugly,” “unpleasant,” “stung my mouth,” “made my tongue tingle,” “almost made my tongue itch,” “made me feel like I was going to gag,” “tasted a little weird,” “made my teeth feel bad,” and “made my mouth feel like it was going to melt.” Many children complained that taking the required number of inhalations was “hard to do” or “a lot to do.” After 5 inhalations, 1 child commented, “I’d rather have it in my leg.”

During the inhalations, 2/11 children in the epinephrine group and 4/8 children in the placebo group coughed, and 3 children in each group experienced dizziness. One child, who was able to inhale almost a full dose of epinephrine (0.096 mg/kg), achieved high plasma epinephrine concentrations and experienced apprehension, nausea, pallor, shaking, and intermittent muscle twitching during the first 50 minutes after the inhalations.

DISCUSSION

This is the first published pediatric study of systemic absorption of epinephrine after inhalation from a pressurized metered-dose inhaler. Before study entry, most of the children had used a metered-dose inhaler regularly for asthma treatment and during the study, they took the epinephrine or placebo inhalations under optimal conditions while being coached by a pediatric allergy nurse. Despite

Fig 1. Concentration versus time plot: mean plasma epinephrine concentrations after inhalation of epinephrine and mean endogenous plasma epinephrine concentrations after inhalation of placebo (vehicle).

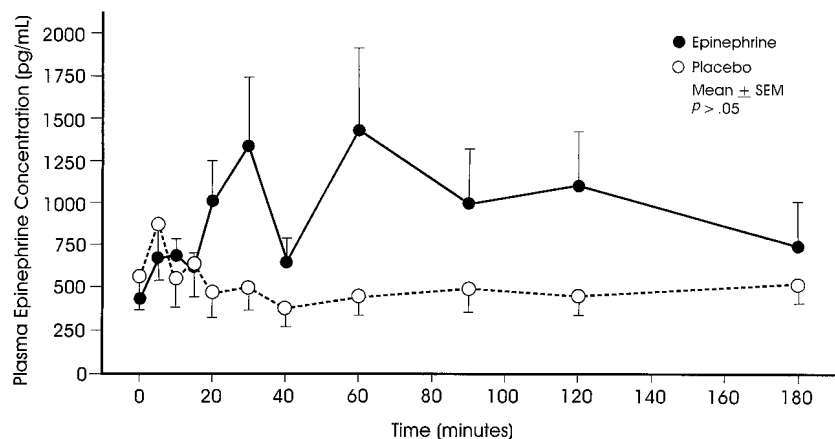


TABLE 2. Heart Rate and Blood Pressure

Time (in Minutes) After Inhalation	Epinephrine	Placebo
Heart rate (beats/min)		
0 (preinhalation)	73 ± 4	74 ± 3
30	76 ± 4	77 ± 4
60	79 ± 3	73 ± 5
120	83 ± 4	79 ± 4
180	80 ± 4	77 ± 3
Systolic (mm Hg)		
0 (preinhalation)	113 ± 2*	105 ± 3
30	121 ± 3*	107 ± 3
60	116 ± 3	107 ± 5
120	115 ± 4	112 ± 5
180	112 ± 2	106 ± 4
Diastolic (mm Hg)		
0 (preinhalation)	66 ± 1	61 ± 3
30	68 ± 1	65 ± 2
60	65 ± 3	62 ± 3
120	68 ± 2*	62 ± 2
180	65 ± 3	59 ± 3

Mean ± standard error of the mean.

* $P \leq .05$.

this, few of them were able to inhale enough epinephrine to increase their plasma epinephrine concentrations promptly and significantly, and complaints about the many inhalations needed and the bad taste of the inhalations were almost universal. In the relatively unsupervised real world situation of an anaphylaxis episode outside a health care setting, it is highly unlikely that a child would manage to inhale as much epinephrine as he or she did under the conditions of this study.

Despite the problems with the inhalations, the mean dose of epinephrine actually inhaled (2.64 ± 0.41 mg) was nearly 10-fold higher than the maximum epinephrine dose of 0.3 mg generally recommended for injection.⁵ High doses are required when epinephrine is administered by inhalation, because the efficiency of pressurized metered-dose inhalers is low and 90% of the dose is swallowed and inactivated by catechol-*O*-methyltransferase and monoamine oxidase in the gastrointestinal tract.¹⁹

Because of the wide range in the dose of epinephrine inhaled (0.75–5.0 mg) and the even wider range of peak plasma epinephrine concentrations achieved (230–4518 pg/mL), the differences in plasma epinephrine concentrations after epinephrine inhalation were not significantly different from baseline epinephrine concentrations or from endogenous epinephrine concentrations after inhalation of placebo. Whether the power of the study is sufficient to be certain that the 2 groups did not differ significantly is difficult to assess. Accurate power calculations were precluded, because they need to be based on previous studies in a similar population in which defined epinephrine doses led to defined increases in plasma epinephrine concentrations. There are no such studies in children. In addition, in this unique exploratory study, because of the difficulties with the inhalations, each child inhaled a different epinephrine dose.

The plasma epinephrine concentrations associated with successful outcome of systemic anaphylaxis treatment have never been defined in any population. In a prospective study of epinephrine injection in children at risk for anaphylaxis, the peak plasma epinephrine concentrations ($C_{\max}$) and time at which peak epinephrine concentrations were achieved ($t_{\max}$) were 2136 ± 351 pg/mL and 8 ± 2 minutes after intramuscular injection and 1802 ± 214 pg/mL and 34 ± 14 minutes after subcutaneous injection. The difference in the time to peak concentrations after subcutaneous injection was statistically significant ($P < .05$) and clinically relevant.⁶ In the present study, the $C_{\max}$ of 1822 ± 413 pg/mL and the $t_{\max}$ of 32.7 ± 62 minutes after epinephrine inhalations were similar to the values achieved after subcutaneous injection in the previous study. The wide range in peak plasma epinephrine concentrations achieved and, especially, the wide range in time to reach peak plasma concentrations with a delay of up to 60 minutes in some children, represent obvious concerns.

The studies in adults in which epinephrine absorption after administration of up to 30 inhalations (3 mg) from a pressurized metered-dose inhaler was compared with epinephrine absorption after subcutaneous injection have yielded conflicting results.^{14–16} One study showed that epinephrine absorption was more rapid and complete after inhalation than after subcutaneous injection, but that with 30 puffs, late-occurring gastrointestinal side effects were dose-limiting.¹⁴ Another study showed that epinephrine absorption was rapid after inhalation, but less complete and shorter-lasting than after subcutaneous injection.¹⁵ A third study showed that systemic absorption of epinephrine was more variable after inhalation than after subcutaneous injection.¹⁶

Ideally, epinephrine studies should be performed in children actually experiencing systemic anaphylaxis; however, prospective, randomized, double-blind, controlled studies of pharmacologic intervention during anaphylaxis are not feasible, because most episodes occur outside a health care setting.^{1–4} In addition, such studies are not ethical, because fatalities or near-fatalities have been reported despite prompt treatment of anaphylaxis.¹

The stated advantages of administering epinephrine via a metered-dose inhaler instead of an injection include: achieving high local concentrations of epinephrine in the airways, lack of pain, low cost, nonprescription availability in many countries, potential for administration of multiple doses, ease of inhalation versus injection, and freedom from adverse effects.^{10–12} In this study, the inability to take the large number of inhalations required, even with the help of a coach, and the complaints about the bad taste and strange sensations in the mouth, tongue, and lips produced by the vasoconstrictor effect of epinephrine on the oropharyngeal mucosa suggest difficulty in administration rather than ease of administration. Furthermore, although epinephrine toxicity is said to be less common when the medication is administered by inhalation than when it is administered by injection,^{15,16} this is not necessarily true, because epinephrine adverse effects are dose-

related pharmacologic effects that occur regardless of the route of administration. The therapeutic dose and the toxic dose are rather similar, as evidenced by symptoms and signs of toxicity observed in one of the few children in our study who was actually able to inhale nearly a full epinephrine dose and achieve high plasma concentrations.

Even a few puffs of inhaled epinephrine might partially or completely relieve upper and lower airway obstruction in anaphylaxis. It is doubtful, however, if relief of hypotension and, most importantly, reduction of mediator release from mast cells, which are epinephrine concentration-dependent,²⁰ would occur in the absence of a prompt, significant increase in plasma epinephrine levels. In a given child, anaphylaxis signs and symptoms are not necessarily identical from one episode to the next and the absence of systemic symptoms, such as hypotension during one episode is not necessarily predictive of the absence of systemic effects during subsequent episodes. In addition, inhalations would not be a satisfactory substitute for injection in any child or adolescent whose symptoms progress rapidly to severe respiratory distress or shock during the 30 minutes or so required to inhale the epinephrine and to achieve peak systemic epinephrine absorption.

CONCLUSION

The potential benefits of epinephrine inhalations for the prehospital treatment of anaphylaxis are outweighed by the lack of feasibility of administering an adequate dose of epinephrine by this route and, consequently, by the likelihood of ineffective treatment. This route of administration is likely to be associated with a falsely high level of security. We therefore urge caution in recommending epinephrine inhalations as a substitute for epinephrine injection for the out-of-hospital treatment of nonrespiratory symptoms in children with anaphylaxis.

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