PEDIATRIC PHARMACOTHERAPY

A Monthly Newsletter for Health Care Professionals from the University of Virginia Children's Hospital

Volume 14 Number 5 May 2008

Self-Injectable Epinephrine for Initial Management of Anaphylaxis in Children

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It has been estimated that 1 to 2% of the population is at risk for anaphylaxis.[1,2] Intramuscular (IM) administration of epinephrine is the primary therapy in the emergency management of anaphylaxis resulting from insect bites or stings, foods, drugs, latex, or other allergic triggers. Its efficacy lies in prompt administration after allergen exposure. Self-injectable epinephrine products have been designed for administration within minutes of the onset of symptoms. In children, these products may be administered by a parent or other trained personnel. This issue of *Pediatric Pharmacotherapy* will review of the role epinephrine in anaphylaxis and highlight current recommendations on the use of self or caregiver-administered epinephrine in children.

Mechanism of Action

Epinephrine is a direct-acting sympathomimetic drug that acts as an agonist at alpha and beta-adrenergic receptors. It produces vasoconstriction to counteract the vasodilation and resulting hypotension associated with anaphylaxis. The bronchodilatory effects of epinephrine and its ability to reduce mucosal edema relieve bronchoconstriction and improve respiratory effort. Epinephrine also down-regulates the release of histamine, tryptase, and other inflammatory mediators from mast cells and basophils, improving respiratory function and reducing the pruritus, urticaria, angioedema, and gastrointestinal symptoms which occur after allergen exposure.[2-6]

Pharmacokinetics

Intramuscular administration of epinephrine into the thigh using an auto-injector results in prompt peak plasma concentrations. In a prospective, randomized, single-blinded study of 17 children between 4 and 12 years of age, Simons and colleagues found that maximum epinephrine concentrations were achieved 8$\pm$2 minutes after injection of a 0.3 mg dose administered into the lateral thigh.[7] In contrast, subcutaneous administration of 0.01 mg/kg epinephrine into the deltoid region resulted in a prolonged absorption, with an average time to peak concentration of 34$\pm$14 minutes (range 5 to 120 minutes; $p < 0.05$). The peak concentrations achieved were not significantly different (2,136$\pm$351 pg/mL in the IM group and 1,802$\pm$214 in the subcutaneous group). The volume of distribution and the terminal elimination half-life for epinephrine in the IM group were 2.0$\pm$1.5 L/kg and 43$\pm$15 minutes, respectively.

After administration, epinephrine is rapidly metabolized in the liver and other tissues. It is methylated to metanephrine or oxidative deaminated then reduced to 3,4-dihydroxyphenyl ethylene glycol or oxidized to 3,4-dihydroxy-mandelic acid.[4-7]

Position Statements and Practice Guidelines

In 2002, the American Academy of Allergy, Asthma, and Immunology (AAAAI) published an updated position statement on the use of epinephrine in the treatment of anaphylaxis.[8] This statement included the following recommendations:

- Prescribers need to be aware of patients' previous allergic reactions. Self-injectable epinephrine should be considered in all patients with a previous history of anaphylaxis or a serious reaction to an allergen. Patients and/or caregivers should be provided with detailed instructions regarding methods for identification and avoidance of allergens, as well as a treatment plan.
- If the patient is not capable of self-administration, epinephrine should be given by any individual recognizing the presence of an emergency need. The Academy supports authorization of trained personnel to administer epinephrine, including lifeguards, teachers, and camp counselors.

- Paramedics should receive training in the recognition and treatment of anaphylaxis. They should be certified to administer epinephrine, based on individual state requirements.
- Intramuscular epinephrine should be included in emergency medical kits in all public facilities.
- It is recommended that epinephrine be available in all schools for use by nurses or other trained staff.

Similar recommendations were published last year by the European Academy of Allergology and Clinical Immunology.[9] Like the AAAAI recommendations, this group supported the use of IM epinephrine as a first-line therapy in children. The group called for the development of anaphylaxis management plans tailored to the individual child, based on previous allergic reactions, other medical conditions, and social circumstances. They recommend that self-injectable epinephrine be prescribed for all children with prior cardiorespiratory reactions, exercise-induced anaphylaxis, idiopathic anaphylaxis, and persistent asthma in children with food allergies.

In March 2007, the American Academy of Pediatrics published a clinical practice guideline on the use of self-injectable epinephrine.[3] This document provides a thorough review of the literature and addresses some of the controversies in the care of pediatric patients, including symptom identification and epinephrine dosing in children weighing less than 15 kg, for whom standard auto-injectors may provide an excessive dose.

Use in Children

While many physicians and nurse practitioners are prescribing self-injectable epinephrine according to these guidelines, the utilization of auto-injectors remains less than ideal. In 2000, Sicherer and colleagues enrolled families of food-allergic children who had been prescribed self-injectable epinephrine into a study evaluating drug knowledge and availability.[10] Of the 100 families evaluated, 86% responded on a questionnaire that they had the device with them at all times, however, only 71% had the device with them at their clinic visit. Of the families who had the device on hand, 10% of the doses had expired. Only 32% of the families were able to correctly demonstrate how to use the device.

In a similar study published in 2006, Arkwright and Farragher interviewed the parents of 122 children previously prescribed an epinephrine auto-injector.[11] Of those completing the survey, 69% were either unable to use the device or did not have it with them at the time of their visit to the allergy clinic. Hands-on training may improve administration skills. Parents who received training during a previous visit were significantly more likely to be able to demonstrate how to use the device than those given only written instructions ($p < 0.005$).

A significant percentage of IM epinephrine doses administered to children are given in the school setting. In a two-year review of 48 school districts in Massachusetts, a total of 115 epinephrine doses were administered, with 91% given by a trained school nurse.[12] Three-fourths of the reactions were considered serious. In 92% of the cases, the child required emergency medical transport to a hospital for further evaluation and treatment.

In spite of this relatively frequent need for epinephrine, many child care centers and schools are not adequately trained or prepared to provide emergency management of anaphylaxis. A survey of school nurses revealed that, although anaphylaxis ranked ninth among school emergencies, only 76% of the schools evaluated had epinephrine auto-injectors available.[13]

In 2006, Patel and colleagues surveyed 39 child care centers 6 months and 1 year after their employees had attended an allergy seminar.[14] There was significant improvement in the caregivers' knowledge about epinephrine after the seminar; however, 6 months later, only 48% of the centers reported that their employees knew how to correctly administer IM epinephrine. This number fell to 31% at the end of a year. The authors concluded that training sessions for child care center personnel provided a significant benefit, but must be periodically reinforced in order to maintain the skill level of the staff.

Contraindications/Precautions

There are no absolute contraindications to the self-administration of epinephrine after a potentially life-threatening allergen exposure. Self-injectable epinephrine should be used with caution in patients with hyperthyroidism, cardiovascular disease, hypertension, or diabetes. Patients who are elderly, pregnant, or less than 15 kg may be at greater risk for adverse effects and should be closely monitored.[4-6]

Adverse Effects

Adverse effects associated with subcutaneous or IM administration of epinephrine include tachycardia, diaphoresis, difficulty breathing, nausea and vomiting, pallor, dizziness, weakness,

tremor, headache, and anxiety. Cardiac arrhythmias and hypertension may occur with unintentional IV administration or overdose.[3-6]

Drug Interactions

Epinephrine should used with caution in patients taking digoxin, quinidine, diuretics, or other alpha or beta-adrenergic agonists, as concomitant administration may lead to arrhythmias or hypertension. The effects of epinephrine may be increased when given with antihistamines, furazolidone, levothyroxine, methyldopa, reserpine, tricyclic antidepressants, or monoamine oxidase inhibitors.[4-6]

Dosing and Administration

The decision to use self-injectable epinephrine should be fully discussed with the patient and/or family. The user should clearly understand the symptoms of anaphylaxis and the need for rapid administration of the drug. The manufacturers of epinephrine auto-injectors provide detailed administration instructions which should be reviewed with the patient or parent. Dey, the maker of EpiPen® and EpiPen® Jr, provides instructions with the product, as well as on their website (www.epipen.com) in both English and Spanish. The website for Versus Pharmaceuticals, the manufacturer of TwinJect®, includes downloadable instructions in English (www.twinject.com). Both websites provide a video clip demonstrating the use of the auto-injector.[2-6]

Epinephrine auto-injectors should be administered intramuscularly into the anterolateral aspect of the thigh as soon as possible after exposure to the allergen. If necessary, the injection may be given through clothing. For adults and children > 30 kg, a dose of 0.3 mg is recommended. A lower dose, 0.15 mg, is recommended for children between 15 and 30 kg. The dose should be approximately 0.01 mg/kg, up to a maximum single dose of 0.3 mg. The dose may be repeated every 10 to 20 minutes as needed until the patient can be seen by a health care provider.[2-6]

Health care providers should be aware of the potential for inadvertent subcutaneous administration with the use of auto-injectors in obese patients. The needle length with the currently available products (typically 1.43 cm) may be inadequate to penetrate muscle in these patients.[2] Prolonged time to peak concentrations may occur, resulting in delayed symptom control.

Epinephrine should not be injected into the buttocks, as absorption may be significantly delayed. Administration into the hands or feet should also be avoided, as it may result in loss of blood flow and tissue necrosis. Inadvertent intravenous administration may result in profound hypertension or pulmonary edema.[4-6]

Epinephrine solutions should be clear; the presence of a pink or brown color indicates oxidation and deterioration of the drug. Discolored solutions or those with a visible precipitant should be replaced. Epinephrine should not be refrigerated or frozen.[4-6]

Availability and Cost

Single-dose epinephrine auto-injectors are available in a 0.3 mg strength (0.3 mL of a 1 mg/mL concentration) and 0.15 mg strength (0.3 mL of a 0.5 mg/mL concentration). The auto-injectors are available in single or double packs with a training injector (for example, the EpiPen® or EpiPen® Jr 2-Pak) or in a two-dose device (Twinject®). Epinephrine auto-injectors should be stored at room temperature and protected from light.[4-6]

The average wholesale price of an EpiPen® or EpiPen® Jr (Dey LP) is $56.54. A kit containing two auto-injectors costs $108.91. The price of the Twinject® 2-dose auto-injector (Verus Pharmaceuticals) is $70.76 for either the 0.3 mg or 0.15 mg strength.[15] A review of local and on-line pharmacies revealed similar prices.

Summary

Self or caregiver-administration of IM epinephrine remains an important first step in the emergency management of anaphylaxis. Recent consensus statements and practice guidelines support its use and highlight the need for increasing accessibility in public settings, such as schools. With implementation of these recommendations, however, comes the need for increased education of patients, parents, educators, and emergency medical personnel.

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Pharmacology Literature Update

Duloxetine in breastmilk

Serum and breastmilk samples were obtained in six lactating women taking the antidepressant duloxetine (Cymbalta®) 40 mg every 12 hours. Their infants were not nursing during the period of drug administration. The mean steady state milk: plasma ratio was 0.25 (90% CI 0.18, 0.35). The amount of duloxetine in the breastmilk was 7 mcg/day, producing an estimated infant dose of 2 mcg/kg/day (range 0.6-3 mcg/kg/day) or 0.14% of the maternal dose. The authors concluded that, although the resulting infant dose may be low, clinicians should be cautious about using duloxetine in nursing mothers when the adverse effects of low-dose exposure remain unknown. Lobo ED, Loghin C, Knadler MP, et al. Pharmacokinetics of duloxetine in breast milk and plasma of healthy postpartum women. **Clin Pharmacokinet 2008;47:103-9.**

Levetiracetam dose titration

This retrospective study describes the use of a rapid levetiracetam titration schedule in children and adolescents with seizures that have not responded to other antiepileptic drugs (AEDs). While the traditional strategy of increasing doses at 2 week intervals remains the most common method for dose titration, there are cases where rapid achievement of full maintenance doses may be needed. The authors of this study have been utilizing rapid titration in selected patients since 2003. They reported the results from eight children, ranging in age from 19 months to 17 years. The levetiracetam dose titration was conducted over a period of 2-14 days, with a mean time to achieve maintenance therapy of 10 days. All of the children achieved at least a 50% reduction in seizure frequency, and six became seizure-free. One patient developed behavioral adverse effects and was taken off the drug after 5 weeks. Her symptoms resolved after discontinuation of the levetiracetam. The authors suggest that rapid titration of levetiracetam may be an acceptable alternative to traditional dose escalation in children who require rapid achievement of therapeutic effect and recommend further study of this approach. Vaisleib II, Neft RA. Rapid dosage titration of levetiracetam in children. **Pharmacotherapy 2008;28:393-6.**

Pretreatment for exercise-induced bronchospasm

The authors of this trial compared the efficacy of inhaled albuterol and oral montelukast in 11 children (7-17 years of age) with exercise-induced bronchospasm. The study was a prospective, randomized, double-blind, double-dummy, cross-over design. Each treatment was administered for 5 days. Serial spirometry was conducted prior to, and at 5, 10, 15, 30, 45, and 60 minutes after exercise. The mean decrease in forced expiratory volume in 1 sec (FEV_1) after exercise was 18.3±13.7% with montelukast, compared to only 0.7±1.6% with albuterol ($p=0.002$). Prevention of exercise-induced bronchospasm, defined as a < 15% decrease in FEV_1 after exercise challenge, occurred in 100% of the patients given albuterol and in 55% of those given montelukast ($p<0.05$). Although this was a very small sample, the authors concluded that albuterol may be a better option for the prevention of exercise-induced bronchospasm in children with asthma. Raissy HH, Harkins M, Kelly F, et al. Pretreatment with albuterol versus montelukast for exercise-induced bronchospasm in children. **Pharmacotherapy 2008;28:287-94.**

Formulary Update

The Pharmacy and Therapeutics Committee did not meeting during April.

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