

Use of epinephrine in the treatment of anaphylaxis

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Purpose of review

This paper is intended to review recent literature that impacts the use of epinephrine in the therapy of anaphylaxis.

Recent findings

The most important recent finding regarding the administration of epinephrine is that the intramuscular route of administration is the route of choice for the treatment of anaphylaxis, and the lateral aspect of the thigh is the site of choice. In addition, recent research emphasizes the fact that epinephrine is grossly underused in the management of anaphylaxis, which accentuates the need for further education of both physician and patient in this regard.

Summary

Several major themes have emerged from this review of the recent literature. The finding that the intramuscular route of administration for epinephrine is superior has now been recognized by the guidelines, and because the site of choice has been found to be the lateral aspect of the thigh, the needle used for injection must be long enough to penetrate the vastus lateralis muscle. The reasons for the underutilization of epinephrine in the treatment of anaphylaxis are also discussed. Other important findings include the fact that outdated EpiPens can usually be administered safely, and alternative routes of administration, which may be more acceptable to patients, may be on the horizon as a result of preliminary studies assessing the administration of sublingual epinephrine by wafer. Finally, it is now understood that epinephrine prescription data may be one of our best tools to study the epidemiology and incidence of anaphylactic episodes.

Keywords

epinephrine, anaphylaxis, anaphylactoid reaction

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Introduction

By consensus, epinephrine is the treatment of choice and the first drug to be administered in the therapy of anaphylaxis. This has been confirmed in every guideline worldwide issued for the management of this condition dating back to at least 1973 [1–10]. However, it must be understood that these guidelines are based on the consensus of expert opinion, and not, in the strictest sense, on evidence-based medicine or outcome studies [11]. The rationale for the use of epinephrine rests mainly on its pharmacology. Therefore, an understanding of the pharmacological effects of epinephrine in relation to its use in the therapy of anaphylaxis is essential.

Pharmacology of epinephrine

The pharmacology of epinephrine is reviewed in detail elsewhere [12], and the summary is taken from the above-noted source.

Epinephrine stimulates both alpha and beta adrenergic receptors. Relative to anaphylaxis, its most important activities occur in the cardiovascular system and the smooth muscle.

When injected intravenously it has an onset of action within seconds. It is extremely important to note that absorption from subcutaneous tissue occurs slowly, probably because of local vasoconstriction, and the drug is much more rapidly absorbed after intramuscular injection. This has been confirmed in adults and children, and the clinical importance of this observation has been documented in a series of experiments by Simons and colleagues [13–15]. On the basis of these observations, the intramuscular route is now the accepted route of administration [8,16*].

Epinephrine produces an increase in blood pressure via its direct effect on the myocardium, which is both inotropic and chronotropic, and by constricting vascular beds especially in the precapillary resistance vessels of the skin, mucosa, and kidney. The main increase in pressure is systolic, and thus the pulse pressure widens. It should be noted that there is marked cutaneous vasoconstriction, a fact that probably accounts for the beneficial effect of epinephrine in the treatment of urticaria and angioedema. It is also important to recognize that coronary blood flow is actually enhanced with the administration of epinephrine [12]. This probably occurs through two mechanisms: the increased relative duration of diastole versus systole, and a dilator

effect resulting from the increased strength of contraction of the myocardium. These effects usually override the direct vasoconstrictor action of epinephrine resulting from the stimulation of alpha receptors in the coronary vessels. These observations give solace to the clinician who is faced with the administration of epinephrine to a patient who has pre-existing coronary artery disease. Nonetheless, myocardial infarction has occurred in both children [17] and adults [18], and myocardial ischemia has been documented as a result of epinephrine administration to a child [19]. However, such ischemia may not be the direct effect of epinephrine on the coronary arteries. It may possibly be the result of other risk factors or arrhythmias that reduce coronary blood flow [20•].

In general, epinephrine dilates smooth muscle. This is of particular importance during anaphylactic episodes with regard to the respiratory tract.

Another possible beneficial effect is the prevention of further degranulation of mast cells and basophils via its beta-adrenergically mediated induction of an increase in intracellular cyclic adenosine monophosphate.

A discussion of the pharmacology of epinephrine is incomplete without mention of the physiological effects of concomitantly administered medications. The potentially deleterious effect of beta blockade has been well noted in a number of case reports describing epinephrine resistant anaphylaxis in patients taking beta blockers [21–25]. However, on the basis of pharmacological studies, the effect of beta blockade can be more complicated than simple epinephrine resistance. For example, the administration of a non-selective beta-adrenergic antagonist such as propranolol, given concomitantly with epinephrine, can actually enhance the vasoconstriction response and the resultant increase in blood pressure. On the other hand, this effect is not noted when a selective beta I antagonist is administered concomitantly with epinephrine. These conflicting activities have produced confusion regarding the administration of epinephrine in the clinical setting to patients who are receiving beta blockers [11]. Some have suggested an increased dose of epinephrine for patients taking beta blockers, whereas others, because of a potential enhancement of the unrestricted alpha effect of epinephrine in this situation, have suggested a decreased dose [11].

Alpha adrenergic blockade has not been documented (to the author's knowledge) to exert a clinical effect after the administration of epinephrine. However, in experimental models, alpha adrenergic blocking agents decrease the pressor effect of epinephrine while enhancing the vasodilation of blood vessels to the skeletal muscles.

The concomitant administration of an alpha adrenergic blocking agent could thus theoretically have an effect on the administration of epinephrine given for anaphylaxis.

In addition, some guidelines mention the potential effect of tricyclic agents such as amitriptyline and monoamine oxidase inhibitors on the clinical effect of epinephrine. Tricyclic antidepressants can potentiate the effect of epinephrine by blocking re-uptake into terminal nerve endings, one of the major routes of physiological inactivation. Monoamine oxidase inhibitors can magnify the activity by preventing the degradation of epinephrine through monoamine oxidase, one of the major systemic metabolic enzymes active in the catabolism of epinephrine. Warnings for both classes of agents with regard to their co-administration with epinephrine appear in the *Physician's Desk Reference* [26].

Underutilization of epinephrine

In spite of the fact that, as noted, by consensus it is well recognized that epinephrine is the treatment of choice, and the first drug to be administered in the therapy of anaphylaxis, it is well documented that this agent is underutilized. The major reasons for the failure of epinephrine to be employed expeditiously involve both physicians and patients [27–45]. For example, Kemp and colleagues [28] found that only 47% of patients who were prescribed epinephrine had their EpiPen injector with them at the time of a recurrent reaction when the etiological agent was known. A greater percentage (89%) maintained the kit on their person when the etiological agent was unknown, the diagnosis being idiopathic anaphylaxis.

Gold and Sainsbury [31] described similar results, finding that prescribed epinephrine was only given to 29% of children with previous anaphylactic episodes. Dily and Roberts [35] made an attempt to assess the reasons why parents did not administer epinephrine to their children experiencing anaphylaxis. They conducted a mail-in survey designed to elicit the reasons for the failure to administer an EpiPen during an event. Only 11 (27% of 41 responders) had used the EpiPen during an attack. Of the 30 who failed to use the EpiPen, 21 (72%) felt that the reaction had not been severe enough. Other reasons included the fact that a hospital was close by (eight), an unexpected trigger caused the reaction, thus producing confusion (six), worry about side-effects (four), and potential pain associated with the injection (three). In two patients the EpiPen was not available. It is clear that more intense patient education can improve adherence to the advice to carry an EpiPen and to use it during an event [27,28]. In an ongoing series of anaphylaxis first reported in 1995 [28] and expanded in 2001 [27], the incidence of non-adherence was reduced from 47 to 33% with a revised educational

protocol emphasizing the importance of keeping the EpiPen available at all times [27].

Physicians also under-prescribe epinephrine. For example, Friesen *et al.* [34] reported a retrospective review of 886 charts taken from a university pediatric emergency department and a regional university emergency department between 1994 and 2001. Only 44% of children and 47% of adults were given epinephrine. In an earlier report [37], they also found that only 14% of children presenting to a pediatric emergency department between 1994 and 2001 received epinephrine before admission. Mehra *et al.* [39], in a study of 32 food-related deaths from anaphylaxis that occurred in Ontario between 1986 and 2000, found that 30 out of 32 individuals had known they were food allergic, and only 11 of these had been prescribed epinephrine. Only four of them had it available at the time of the reaction, and in one instance the device had expired 2 years previously. Clark *et al.* [40] found that only 80% of patients presenting with bee sting allergy in an emergency room received epinephrine, and only 11%, upon discharge from the emergency department, were given a prescription for self-injectable epinephrine.

In addition, even when patients are prescribed epinephrine, administration errors caused by incorrect technique can occur partly because physicians, nurses, and emergency medical technicians are not facile with the technique of administration, thus instructing patients incorrectly, or simply fail to give instructions regarding the use of an automatic epinephrine injector [29,36,38]. In one study involving emergency room physicians, pediatricians, and family practitioners [30], only a quarter could demonstrate the proper technique for use, and only 14% had a placebo to demonstrate the correct usage. Sicherer *et al.* [29] documented similar results in a study of pediatricians. In a study of 78 senior house officers [46], although all knew that epinephrine should be administered, 55% did not know the preferred route and only 5% knew both the correct route and dose.

Other problems associated with the outpatient administration of epinephrine

As noted above, patients often do not adhere to recommendations regarding the use of epinephrine. In addition to not keeping the epinephrine with them, they often do not refill the prescription at the appropriate time. This leads to epinephrine injectors not infrequently being out of date at the time of need [39]. Simons *et al.* [47] addressed this issue by evaluating outdated EpiPen kits. They found that the auto-injectors were still intact although the plastic sheaths showed signs of wear. In most instances the epinephrine was not discolored and no precipitants were visible. Nonetheless, the bioavailability was significantly re-

duced. The loss in bioavailability, as expected, correlated with the duration of time that had passed since the expiration date. However, regardless of these findings, the injectors still retained some degree of potency. The authors thus recommended that as long as the epinephrine is not discolored and does not contain precipitants, it should be administered [47].

Another problem centres on the fact that the most commonly prescribed method of self-administration of epinephrine, the EpiPen, does not allow for dosage flexibility in children. This can result in overdosing in the pediatric patient [48,49].

Finally, another problem regarding outpatient administration is the fact that epinephrine, although a potent therapeutic agent, is not universally effective as monotherapy. These investigations have shown that even when administered in the normally recommended dose, in a timely fashion, fatalities can still occur [41,44,50]. In a recent study of hypotensive anaphylactic shock in a dog model [51], epinephrine was ineffective by any route when administered at the nadir of the reaction. This observation is reflected in a well-documented report of epinephrine-resistant anaphylaxis occurring after insect sting challenge [52].

Dosages and routes of administration

As noted previously, pharmacokinetic studies [12–15] have clearly documented that, in the outpatient setting, the intramuscular route of administration is the route of choice because of slowed absorption, probably due to vasoconstriction, when the drug is administered subcutaneously. The site of choice because of its vascularity is the lateral aspect of the thigh (as opposed to the traditional site, the deltoid) [14,15]. The traditional initial dose in the adult is 0.3–0.5 ml of a 1 : 1000 dilution (0.3–0.5 mg) [53]. However, doses of up to 1 mg have been recommended in the European Guidelines [6]. Children 12 years of age and older (unless particularly small) should also receive a dose of 0.3 mg. Recently, a dosage schedule for younger children has been recommended [7] as follows: children 6–12 years, 0.25 ml (0.25 mg); children between 6 months and 6 years of age, 0.12 ml (0.12 mg); and infants less than 6 months of age, 0.05 ml (0.05 mg). As has been noted, the use of an EpiPen Jr, which contains 1.5 mg and is the smallest dose available in an EpiPen, would result in the overdosage of children under 6 years of age, according to the above published guidelines.

The alternative to the administration of an automatic injector would be to prescribe a vial of epinephrine along with a syringe. There are, however, great difficulties in doing this because such epinephrine products go out of date rapidly, should not be exposed to the sunlight or

heat, and the technique required for administration using a syringe and ampoule is difficult, especially when the parent is under stress. Simons *et al.* [54] prospectively evaluated this technique, and found that the use of a syringe and ampoule caused more errors in dosing and delayed administration.

Epinephrine has been successfully administered by other routes, including sublingual injection and via an endotracheal tube. These can be employed in a case of severe anaphylaxis when intravenous access cannot be obtained [53]. Intravenous access should be reserved for severe cases when the patient has been unresponsive to intramuscular injection. There is no established dose and numerous regimens have been recommended [55–58]. Treatment protocols are different for anaphylaxis than for cardiac arrest. Regardless of the dose and regimen employed, care must be taken and the patient should be monitored for arrhythmias. One suggested protocol for anaphylaxis is as follows: An intravenous preparation can be prepared by diluting 0.1 ml (100 µg) of a 1 : 1000 w : v (1 mg/ml) aqueous epinephrine solution in 10 ml normal saline. The 10 ml dose can be infused over 5–10 min, resulting in a total dose of 100 µg at a rate of 10–20 µg/min. This can be repeated depending on the response [53–55].

There is some indication that inhaled epinephrine, via commercially available metered dose inhalers, is still being employed [59]. Although there are data supporting the use of inhaled epinephrine [60], administration of the preparations currently available is not recommended for several reasons: an impractically large number of inhalations are required to achieve an adequate dose, the taste of the preparation makes it difficult to achieve this number, and there are well-known difficulties in mastering the required inhalation technique [61]. Nonetheless, the inhaled route might be feasible via alternative preparations designed to deliver larger doses via different formulations (e.g. powder).

A sublingual tablet has recently been found to be effective in an animal model, and the sublingual route might be a suitable alternative to injected epinephrine [62]. In this model it was demonstrated that a sublingual tablet can result in a high, rapidly achieved peak epinephrine plasma concentration that is similar to those that occur after intramuscular epinephrine.

Epinephrine prescriptions used to study the incidence of anaphylaxis

An unexpected benefit of the EpiPen is the ability to use prescriptions issued for EpiPens to establish the incidence of anaphylaxis. This method, which employs real-time data collected from pharmacies, may be the most accurate assessment of the incidence of anaphylaxis

that is available. Most of the studies have been carried out by Simons and colleagues in Canada [48,63,64], but recently similar data has been collected from Wales [65]. The data collected from Canada found that 1.2% of the pediatric population received EpiPen prescriptions. For the entire Manitoba population (children and adults), the incidence of prescriptions was 0.8%. The data from Wales found that EpiPen and EpiPen Jr prescriptions were given in 0.2 per 1000 population, and the incidence of prescribing these injectors had increased markedly between 1994 and 1999. Of parenthesis interest is that in both studies, EpiPen prescriptions were given in increased amounts in higher income populations. In the Canadian study, this pattern persisted irrespective of whether or not the patients had access to specialist care.

Conclusion

The first drug and the drug of choice utilized in the treatment of anaphylaxis is epinephrine. Epinephrine should be administered by deep intramuscular injection in the vastus lateralis muscle located on the lateral aspect of the thigh. Recent observations regarding the appropriate and timely use of the administration of epinephrine via this route indicate that the drug is greatly underused. The reasons for this are complex, but both physicians and patients bear responsibility. The upshot of this observation is that physicians should redouble their efforts to emphasize the importance of patients refilling their prescription when it becomes outdated, keeping their medication with them at all times, and using their EpiPen in a timely and appropriate fashion. Also, there is an ongoing problem regarding the outpatient administration of epinephrine to children, in that there is not a great enough variety of doses to allow the physician to administer the currently suggested dosage regimen. Finally, it is anticipated that more easily administered dosage routes will be developed. One of the most promising at this time is the sublingual route via a wafer.

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