Epinephrine, anaphylaxis, and biphasic reactions

Introduction

1. Anaphylaxis is a life-threatening, IgE-mediated allergic reaction most commonly triggered by medications, foods, and stinging insects.
2. Symptoms occur rapidly, within minutes up to as late as 1 hour, and can involve urticaria, angioedema, dyspnea, hypotension, nausea/vomiting, and abdominal pain among many other reactions.
3. Some patients experience biphasic anaphylaxis, which is recurrent anaphylaxis that occurs an average of 10 hours (1 to 72 hours) after the resolution of the initial episode. Mechanisms of biphasic anaphylaxis are poorly understood.

Pharmacology	
Epinephrine	
Role in Therapy	First-line therapy for uniphasic and biphasic anaphylaxis
Mechanism	Non-selective α- and β-adrenergic agonist • **α_1 receptor:** vasoconstriction that alleviates hypotension, erythema, urticaria, angioedema, and upper airway mucosal edema • **β_2 receptor:** bronchodilation and suppression of further mediator release from mast cells and basophils • **β_1 receptor:** increases heart rate and contractility

Intramuscular Administration	Dose
	• 0.3 to 0.5 mg **OR** 0.01 mg/kg (max 0.5 mg in adolescents & adults; max 0.3 mg in children) IM every 5 to 15 minutes
	• Use 1 mg/mL epinephrine concentration
	Route
	• Administer intramuscularly into the anterolateral aspect of the thigh [refer to literature section]
	  ○ IM absorption > subcutaneous (SQ) absorption
	  ○ Thigh absorption > deltoid administration

Intravenous Epinephrine	Indications
	• Inadequate response to multiple IM epinephrine injections
	• Hypotension unresponsive to fluids
	• Cardiac or respiratory arrest
	Dose
	Hemodynamically Stable
	• Initial: 1 mcg/min IV continuous infusion titrated by 0.5 mcg/min every 10 to 15 min to desired response
	• Administration:
	  ○ ***Fluid-Resuscitated:*** Inject 1 mg (1 mg/mL) epinephrine into 250 mL of NS or D5W and start infusion at 15 mL/hour (= 1 mcg/min) and titrate by 7.5 mL/hour (= 0.5 mcg/min)
	  ○ ***Requires Fluid Resuscitation:*** Inject 1 mg (1 mg/mL) epinephrine into 1 L of NS or D5W and start infusion at 60 mL/hour (=1 mcg/min) and titrate by 30 mL/hour (= 0.5 mcg/min)
	Anaphylactic Shock
	• Initial: 2 to 10 mcg/min titrated every 10 to 15 min to desired MAP (max 1 mcg/kg/min) with appropriate fluid resuscitation
	• Administration: Epinephrine premixed 8 mg/250 mL [specific to Grady Health]

Adverse Effects	Tachyarrhythmias, hypertension, myocardial ischemia, mesenteric ischemia, extravasation, lactic acidosis
Glucocorticoids	
Role in Therapy	Limited role in acute treatment of anaphylaxis
Mechanism	Bind to the glucocorticoid receptor on cell membranes and inhibit gene expression and production of new inflammatory markers
Dose	Methylprednisolone (Solu-Medrol) 50 to 125 mg IV x 1 dose given after epinephrine
Onset	Hours to prevent transcription and translation of inflammatory markers
Histamine Receptor Antagonists	
Role in Therapy	Adjunct secondary to epinephrine to treat urticarial, pruritus, and flushing
Mechanism	Inhibits the effect of released histamine at the H1/H2 receptors
Dose	H1 Receptor Antagonist • Diphenhydramine (Benadryl) 25 to 50 mg IV x 1 dose given after epinephrine H2 Receptor Antagonist • Famotidine (Pepcid) 20 mg IV x 1 dose given after epinephrine
Onset	Peak plasma concentrations are not reached until 60-120 minutes after administration

Literature			
Author, year	**Design**	**Purpose**	**Outcomes**
Route of Epinephrine Administration			
Simons et al. 1998	RCT (N=17)	Evaluate epinephrine absorption between IM and SQ routes in children	**-IM injection of epinephrine led to a faster peak epinephrine concentration than the SQ route** (8 min vs. 34 min)
Simons et al. 2001	RCT (N=13)	Evaluate the optimal route and site of epinephrine injection in adults [see figure below]	**-Mean epinephrine peak plasma concentration higher after epinephrine IM injection into the thigh** than SQ injection or IM injection into the deltoid (9722 pg/mL, 2877 pg/mL, and 1821 pg/mL, respectively) **-Peak epinephrine concentration with IM injection around ~10 minutes**
Brown et al. 2004	Prospective cohort study (N=19)	Assess sting anaphylaxis management with carefully titrated IV epinephrine infusion (5-15 mcg/min titrated to response) and volume resuscitation	-18/19 patients responded with symptomatic improvement and SBP >90 mmHg within 5 min -No adverse reactions attributable to epinephrine -Median total dose of epinephrine was 590 mcg (190-1310 mcg) and median total infusion duration was 115 min (52-292 min)
Glucocorticoids & Antihistamines in Biphasic Anaphylaxis			
Grunau et al. 2015	Retrospective cohort study (N= 473)	Determine the association of steroid administration with decreased relapses in ED allergy patients	**-4 biphasic reactions occurred in the steroid group and 1 in the non-steroid group** **-No difference in revisits during 7-day follow-up period** between steroid and non-steroid group (5.8% vs. 6.7%)
Ko et al. 2015	Retrospective cohort study (N= 415)	Determine prevalence and clinical characteristics of biphasic reactions in patients treated with steroids	-Biphasic reactions occurred in 9/415 (2.2%) patients **-No difference in epinephrine use or H1 blocker use between those that did or did not develop a biphasic reaction**

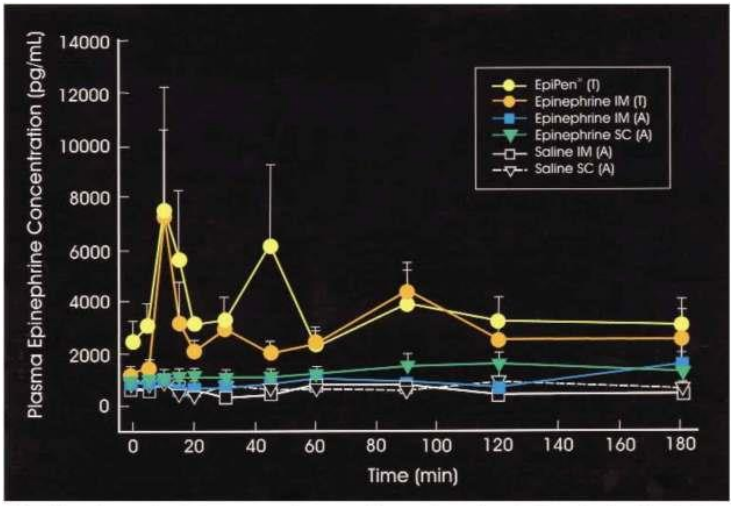

FIG 1. Mean plasma epinephrine concentrations versus time are shown after administration of an identical 0.3-mg (0.3-mL) dose of epinephrine by IM or SC injection in 2 different sites. *T*, Thigh; *A*, upper arm. Mean endogenous plasma epinephrine concentrations are shown after IM or SC injection of 0.9% saline solution (0.3 mL) in the upper arm. The plasma epinephrine concentrations shown were calculated by averaging (mean ± SEM) the epinephrine concentrations at each sampling time for each route and each site of injection.

Conclusion

1. Epinephrine is the cornerstone of therapy in anaphylaxis, and delayed use of epinephrine has been associated with an increased rate of mortality.
2. **Do not delay the administration of epinephrine** for the administration of histamine receptor antagonists or glucocorticoids.
3. Continuous epinephrine intravenous infusions may be started in patients that do not respond to multiple doses of IM epinephrine, have persistent hypotension, and cardiac and/or respiratory arrest.
4. Histamine receptor antagonists and glucocorticoids do not prevent biphasic anaphylaxis, and patients should be counseled on this recurrent reaction.

References

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