Epinephrine in Paediatric Clinical Practice - Clinical Update

Anwarul Haque[1], Hassaan Sadiq[2], Muhammad Abdullah[3], Hassaan Khan[4], Sadiq Mirza[5]

Abstract

Epinephrine is a "friend of the doctor" because it is a life-saving drug used in the rescue of patients at difficult times when other things do not help. It is widely used in paediatric emergency and paediatric intensive care units. This short commentary on pharmacology provides a clinical update about the use of epinephrine in paediatric clinical practice. The first part of this article briefly reviews the clinical pharmacology and the second part describes the clinical indications and adverse effects of epinephrine.

Keywords: Epinephrine, cardiopulmonary resuscitation, anaphylaxis, child, paediatric medicine, pharmacology

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Introduction

Epinephrine is also called adrenaline, which was first isolated in 1874. It is a life-saving drug. It is an endogenous catecholamine which acts as a hormone and neurotransmitter. It is synthesised from tyrosine in the adrenal medulla and released into the blood circulation. It has a wide range of effects throughout the body including the heart, blood vessels, smooth muscles and metabolic effects. It maintains "interior milieu" in the body in time of stress and emergency and has a vital contribution in the fight-or-flight response. However, being a polar compound it does not cross the blood brain barrier[1]. This review has two components: pharmacology and clinical consideration. Epinephrine mainly acts as an inotrope and as a vasopressor. The rationale of writing this mini-review is that epinephrine is one of the most important and life-saving drug used in emergency room and Paediatric Intensive Care Unit (PICU), but majority of our medical and paramedical staff is unaware of the pharmacological effects, side effects, dosage, preparations, indications and mode of administration of epinephrine.

There are various routes of administration of epinephrine. It can be given intravenously, intramuscularly, subcutaneously, by endotracheal tube, and by inhalation. Catecholamine is inactivated in the intestine by intestinal enzymes, hence their oral administration is not effective. The half-life of epinephrine is 2-3 min. It is rapidly metabolized in the liver by two enzymatic pathways: monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT), and excreted through the kidneys. Only a small amount of epinephrine may appear in urine of a normal person as normally only the metabolites are excreted. The final metabolites that appear in

[1] Dept. of Paediatrics, AKUH, Karachi
[2] MBBS Student, Dow University of Health Sciences,
[3-4] MBBS Student, Aga Khan Medical College, Karachi
[5] Dept. of Paediatrics, Abbasi Shaheed Hospital, Karachi

Correspondence: Dr. Sadiq Mirza
Department of Paediatrics, Abbasi Shaheed Hospital
Email:drsadiqmirza@hotmail.com
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the urine include metanephrine and vanillylmandelic acid[2].

Epinephrine's pharmacologic activity is primarily in the autonomic nervous system. It increases the chronotropic and inotropic actions of the heart. The effects of epinephrine on the smooth muscles of different organs and systems depend on the type of adrenergic receptor in the muscle. It causes vasoconstriction by stimulation of α_1 receptors and vasodilation via stimulation of β_2 receptors. At therapeutic doses, blood flow to skeletal muscles is increased. Arterial and venous pulmonary pressures are raised and coronary blood flow is also increased by epinephrine. It increases the concentrations of glucose and lactate in blood by inhibiting insulin and by increasing glucagon secretion. It also raises the concentration of free fatty acids in the blood[1,2].

Epinephrine is available in following preparations, as injection, 1:1000 aqueous (1 mg/ml) and 1:10,000 aqueous (0.1 mg/ml). Also as an IM auto injector, 0.15 mg and 0.3 mg while the racemic solution is 2.25%.

Clinical Indications for the use of Epinephrine include

Resuscitation

Epinephrine is a standard drug of cardiac resuscitation for many decades. It is indicated for non-shockable rhythm i.e. asystole, pulse-less electrical activity, for shockable rhythm i.e., ventricular fibrillation, pulseless ventricular tachycardia. It is also indicated for paediatric bradycardia if there is cardiopulmonary compromise and heart rate persists <60/min even after cardiopulmonary resuscitation (CPR). Epinephrine acts through alpha-receptors which augment coronary blood flow for restoration of cardiac activity[3,4]. Several observational reports confirm that epinephrine administration during cardiopulmonary resuscitation can increase the chances of return of spontaneous circulation (ROSC), but no benefits in long term survival in adult patients[5,6]. There is no such data available in paediatric patients. Current American Heart Association (AHA) guidelines recommend that the standard intravenous dose of epinephrine is 0.01 mg/kg (0.1 ml/kg of 1:10000 solution) followed by a flush of normal saline and this can be repeated after every 3-5 minutes (or alternate cycle) along with chest compression and positive pressure ventilation. The standard intravenous adult dose is 1 mg. It can also be given through intraosseous line when intravenous line is not accessible. Intratracheal dose of epinephrine is 10 times of IV dose (i.e. 0.1 mg/kg or 0.1 ml/kg of 1:1000 concentration)[4]. Intatracheal dose is no longer recommended because of its variable absorption and poor efficacy. The high dose (mega dose) of epinephrine is not superior to standard dose of drug and is not recommended. High-dose is associated with myocardial necrosis and may be harmful[7]. Intracardiac dose is also not recommended.

Anaphylaxis

Epinephrine is widely advocated as the first line treatment for anaphylaxis[8]. A physician or other healthcare professional can manage this initial emergency treatment when anaphylaxis occurs in a healthcare setting[9]. In this setting, intramuscular (IM) or intravenous (IV) infusion or both routes for adrenaline are preferred. Simon et al studied the rate of epinephrine absorption in children and compared the subcutaneous route versus the intramuscular route[10]. The mean maximum plasma epinephrine concentration with subcutaneous (SC) drug injection peaked in 34 ± 14 minutes versus 8 ± 2 minutes for the IM route. This study changed the way epinephrine was administered in the paediatric emergency department. Intramuscular injection is currently the standard route of epinephrine administration for acute anaphylaxis.

At recommended dosages and routes of administration, the adrenergic vasoconstrictive effects reverse peripheral vasodilation, which alleviates hypotension and also reduces erythema, urticaria, and angioedema. Local injection of epinephrine may also minimize further absorption of antigen from a sting or injection, but this has not been studied

Table 1. Epinephrine: Indications route and dose.

INDICATION	ROUTE	DOSE	COMMENTS
Resuscitation: Asystole/Pulseless Electrical Activity/Bradycardia with hypoperfusion/Ventricular Fibrillation (VF) or Pulseless Ventricular Tachycardia	Intravenous Injection	0.01mg/kg (0.1 ml/kg of 1:1,10,000 standard concentration) IV/IO q 3 to 5 minutes Repeat on alternate cycle (max single dose 1 mg)	•During first cycle in Asystole/ PEA After each administration, followed by 10 ml saline flush • After 2nd shock in VF • After First 2-min cycle of CPR in Bradycardia with hypoperfusion
Anaphylaxis	Intramuscular injection	*IM autoinjector 0.3 mg (for patient ?30 kg) or IM junior autoinjector 0.15 mg (for patient weighing 10 to 30 kg)	• Preferred site is Vastus lateralis.
		* 0.01 mg/kg (0.01 ml/kg of 1:1000 high concentration) IM q 15 minutes PRN(max single dose 0.3 mg)	
		* 0.01 mg/kg (0.1 ml/kg of standard conc.) IV/IO q 3 to 5 minutes(max single dose 1 mg) if hypotensive	
		* 0.1 to 1 mcg/kg per minute IV/IO infusion if hypotension persists despite fluids and IM injection.	
Shock: Septic shock Low Cardiac Output Syndrome (LCOS)	Intravenous infusion	0.1 to 1 mcg/kg/min IV/IO infusion (consider higher doses if needed)	Prepare by adding required dose of epinephrine in 50 ml of NS, D5w or D10W
Respiratory illnesses: Post-extubation stridor Bronchiolitis, Croup,	Via inhalation	* 0.5 ml/kg of regular epinephrine (1-3 ml) mixed with 3 ml of normal saline via inhalation * 0.25 to 0.5 mg racemic solution (2.25%) mixed in 3 ml NS via inhalation.	
Adjunctive of Local Anaesthetic	Via infiltration		Along with local anaesthetic to prolong the effect of Epinephrine

systematically. Rapid achievement of peak plasma and tissue epinephrine levels seems to optimize survival because retrospective human studies demonstrate that delayed administration is associated with poor outcomes[6,7]. Reasons may be multifactorial and include delayed administration, inadequate doses, inappropriate route of administration, use of epinephrine that has passed its expiry date, leading to inadvertent administration of an inadequate dose, or an underlying disease, such as poorly controlled asthma, cardiovascular disease, mastocytosis, and perhaps other serious systemic disorders[8,9].

Expert consensus and anecdotal evidence indicate that aqueous epinephrine 1:1000 dilution (1 mg in 1 mL), 0.2 to 0.5 mg (0.01 mg/kg in children; maximum dose, 0.3 mg) administered intramuscularly every 5 to 15 minutes or as necessary, depending on the severity of the anaphylaxis, should be used to control symptoms and sustain or increase blood pressure.

When anaphylaxis occurs in the community, in a non-medical setting, the standard of first-aid treatment is the administration of self-injectable epinephrine into the anterolateral thigh using an EpiPen (also called Fastject), Anapen, AnaHelp, Fastject, or other adrenaline formulations[11].

Epinephrine in therapeutic doses stimulates á$_1$ adrenergic receptors which results in vasoconstriction, increased peripheral vascular resistance and decreased mucosal oedema. It also activates â$_2$ adrenergic receptors which results in bronchodilation and decreased mediator release from mast cells and basophils[12]. Low epinephrine concentrations may paradoxically increase the release of histamine and other mediators from mast cells and basophils and result in vasodilation.

Epinephrine as an inotrope in different types of shock.

Epinephrine is indicated in different types of shock based on clinical evidence of haemodynamic parameters[13]. Latest published guidelines on clinical practice guidelines on paediatric severe sepsis and septic shock from American College of Critical Care of Medicine (ACCM) recommended epinephrine as the drug of choice for fluid-refractory cold shock and can be given througha peripheral vein while getting central venous access to avoid delay in optimisation of haemodynamics[14,15]. Many published reports have shown that delay in reversal of shock is associated with higher mortality, while on the other hand, rapid diagnosis and quick reversal of shock is associated with improved outcomes.

Epinephrine is also indicated in low cardiac output syndrome resulting from various causes. Many centres use low-dose epinephrine as initial inotropic agents in postoperative care of children after cardiac surgery in intensive care units. It is also used in other forms of acute decompensated heart failure refractory to routine treatment, like post-arrest myocardial depression, depressed myocardium secondary to environmental agents like drugs and viruses[15,16]. Epinephrine is used in conditions to optimise haemodynamics and improve oxygen delivery to tissues especially in unavailability of mechanical circulatory support. However, there is a high risk of cardiac arrhythmias and myocardial necrosis.

Status Asthmaticus

Epinephrine is not considered in initial management of acute severe asthma in children. The availability of recent selective â$_2$-agonist as nebulizer solution as well as parenteral solution in the treatment of acute severe asthma has replaced epinephrine. Epinephrine is considered as obsolete therapy for asthma. It is only recommended for life-threatening situation[17].

Bronchiolitis

Bronchiolitis is the most common cause of acute illness of lower respiratory tract infections and hospitalization for infants and young children worldwide[18]. The role of epinephrine in treatment of acute bronchiolitis remains controversial[19]. Several reports and meta-analysis demonstrated conflicting results[20,21]. However, a recent trial showed a shorter length of hospitalization when nebulized epinephrine was given on demand instead of fixed schedule treatment[22].

Upper Airway Obstruction

Nebulised epinephrine has been indicated in upper airway obstruction due to croup syndrome and post-obstruction stridor for many decades. Epinephrine exerts its effect through reduction in airway oedema and dryness from airway secretions[23]. In a Cochrane systemic review, eight studies (225 patients) were evaluated and found that there was a significant reduction in severity of respiratory symptoms after nebulisation of epinephrine. It has also been demonstrated that there is no difference in clinical effect between the two types of nebulized racemic and regular injectable L-epinephrine. The combination of nebulised epinephrine and steroid are known to improve post-extubation stridor and prevent from reintubation.

Toxins/Overdose (e.g.â-Adrenergic Blocker, Calcium Channel Blocker)

Epinephrine is used IV/IO in a dose of 0.01 mg/kg (0.1 ml/kg of 1:10000); if no response, consider higher doses up to 0.1 mg/kg (0.1 ml/kg of 1:1000). Epinephrine can also be used as IV/IO infusion in a dose of 0.1 to 1 mcg/kg per minute infusion (consider higher doses if hypotension refractory to this dose).

Adjunct of Local Anaesthetic

Addition of very low-dose epinephrine to local anaesthetic provides vasoconstriction to decrease bleeding, prolongs duration of analgesia and reduce systemic dose of local anaesthetic toxicity. However, use of epinephrine is avoided in distribution of end arteries like toes, finger, ear, nose and penis[9].

Table 1 summarises the dose, route and indications of use of epinephrine in paediatric clinical practices.

Adverse Effects of Epinephrine

Each drug has adverse effects. The adverse effects related to epinephrine are divided into three components[9]. There are 54 drugs and drug classes specifically reported to interact with epinephrine. Some are worth noting. Patients taking tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), or levothyroxine may experience greater and longer lasting effects of epinephrine.

Beta blockers may lessen or interfere with the therapeutic effects of epinephrine. Patients with hyperthyroidism, cardiovascular disease, diabetes, hypertension, pregnancy, or those weighing less than the recommended weights (30 kilograms for EpiPen and 15 kilograms for EpiPen Jr.) are at greater risk of developing side effects or adverse reactions.

CNS: It can cause apprehension, agitation, anxiety and tremor, dizziness, headache, drowsiness, confusion, hallucination, intracranial haemorrhage (from severe hypertension).

Cardiac: Increase in blood pressure and heart rate is normal physiological effect of epinephrine. The cardiac arrhythmias especially ventricular arrhythmia is a serious complication of epinephrine.

ST-segment elevation and post-resuscitation myocardial dysfunction are known complications. High-dose and prolonged use of epinephrine can lead to progressive myocardial damage including necrosis and cell death.

Respiratory: Dyspnoea is a known adverse effect.

Gastro-intestinal: Nausea and vomiting.

Genito-urinary: Renal vascular ischemia.

Electrolytes: ($â_2$-adrenergic stimulation causes intracellular potassium shift).

Metabolic Effects: Hypokalaemia and hyperglycaemia are the most common metabolic side effects of epinephrine. Lactic acidosis also occurs when epinephrine is infusedin the management of shock.

Skin Necrosis: When epinephrine is used with local anaesthetics in area of end arteries as well as extravasation from peripheral vein.

Miscellaneous: Gluconeogenesis response increases serum lactate independent of any change in organ perfusion, making interpretation of serum lactate as a marker of ischemia more difficult.

Monitoring: Monitor electrocardiogram (ECG) and peripheral capillary oxygen saturation (SpO2) continuously and blood pressure frequently. When tapering the dose of epinephrine these parameters are strictly monitored.

Precautions while using Epinephrine

- High doses produce vasoconstriction and may compromise organ perfusion.
- Low doses may increase cardiac output with redirection of blood flow to skeletal muscles, producing decreased renal and splanchnic blood flow.

" Myocardial oxygen requirement is increased (as the result of increased heart rate, myocardial contractility, and with higher doses, increased systemic vascular resistance (SVR).

" Tissue ischaemia and necrosis may result if IV infiltration occurs. Infiltration with phentolamine may reduce local toxic effect of epinephrine.

" Central venous access is preferred for administration.

" Catecholamines are inactivated in alkaline solutions.

" Observe at least 2 hours after croup treatment for "rebound" (i.e., recurrence of stridor).

Contraindications for the use of epinephrine include cocaine-induced ventricular tachycardia.

Conclusion

Epinephrine is a sympathomimetic drug, which has a primary role in reversal of anaphylactic reaction and cardiac arrest. It can be safely used in other conditions with cautions.

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