

Epinephrine

Synonyms: adrenaline; catecholamine.

CAS: 51-43-4

MF: C₉H₁₃NO₃

MW: 183.2

Solubility: slightly soluble in water (1 g/l, at 25°C); slightly soluble in alcohol; readily soluble in aqueous solutions of mineral acids [1].

Major uses

Epinephrine is a natural catecholamine, derived from the amino acids phenylalanine and tyrosine. It was described in 1895, and first artificially synthesized in 1904. It is used in the management of anaphylactic reactions and cardiac resuscitation. It is also used for treatment of asthma and glaucoma, in surgical procedures on nose, throat and larynx; in immunotherapy (e. g. treatment of allergy); as well as for treatment of some other health conditions [1, 2].

Human toxicity

Epinephrine is a hormone normally presenting in the body at low concentrations, but its level in plasma is elevated in various physiologic conditions, as well as at several diseases, and at stress situations. Epinephrine plasma level from 60 normal resting subjects was 0.034 ± 0.002 ng/ml (mean \pm SEM); norepinephrine 0.228 ± 0.01 ng/ml; acute maximal stress (resuscitation following cardiac arrest) resulted in a greater than 300-fold increase in the plasma epinephrine level (10.3 ± 2.9 ng/ml; range 0.36 to 35.9; n=15; p<0.01) [3]. In another study, epinephrine level in normal subjects (n=10, males, age 24-33 years, a mean year of 27 years) was reported to be 0.037 ± 0.006 ng/ml [4].

Recommended therapeutic dosage of epinephrine for allergic emergencies is 0.1 to 0.3 mg as a subcutaneous injection. For treatment of myocardial infarction or cardiac arrest (resuscitation efforts) a dosage of 0.5 to 1 mg every 5 min is recommended [5].

Epinephrine may be toxic and even fatal at elevated levels. The cases of intentional poisoning are rather rare; however, there are numerous of overdose given by erroneous dilution of epinephrine preparation in the hospital.

Some clinical adverse effects are listed here:

a) cardiovascular: hypertension, or hypertension followed by profound hypotension; myocardial ischemia or infarction; dysrhythmias, and vasoconstriction; b) respiratory: pulmonary edema, pneumothorax, cyanosis, and pulmonary embolism; c) neurologic: anxiety, nervousness, palpitations, and numbness of hands and feet; tremors, insomnia, and headache; d) gastrointestinal: nausea, vomiting, and abdominal pain are common following epinephrine overdose; e) metabolic acidosis and lactic acidosis. Death after epinephrine overdose is mostly caused by either cerebral hemorrhage or cardiac arrest/arrhythmia [2].

The maximum tolerated dose of subcutaneously injected epinephrine has been estimated to be 7 to 8 mg. The minimum lethal human epinephrine dose by subcutaneous injection has been estimated to be 4 mg. [2]. However, survival was reported after 50 mg of adrenaline administered subcutaneously [6]. Several fatal cases have been earlier described after acute epinephrine doses of 8-75 mg [7], however, blood concentration data are missing.

In subjects with normal cardiovascular function, after intravenous infusion of 0.00005 mg/kg/min epinephrine during 14 min, the mean plasma epinephrine level was 0.000259 ± 0.000024 mg/l [4].

The mean plasma levels of 0.01 mg/l for epinephrine and 0.007 mg/l for norepinephrine could produce significant cardiovascular and metabolic toxicity in healthy people [3].

Toxicity of epinephrine is increased in the presence of hyperthyroidism, angina, and the co-administration of some drugs, e.g. reserpine, cyclopropane, and chloral hydrate [2].

Kinetic data

Absorption: Epinephrine is not effective after oral administration because it is rapidly conjugated and oxidized in the gastrointestinal mucosa and liver. Absorption is more rapid after intramuscular than after subcutaneous injection [5].

Epinephrine is rapidly inactivated in the body. Infusion of epinephrine that resulted in levels less than 0.1 ng/ml has produced mean plasma half-life of 1.68 ± 0.16 min [8]. In another study, the plasma half-life was estimated to be 8 min after standard dose of 1 mg, as well as after high dose of 0.2 mg/kg. The highest arterial level may have occurred earlier than 2.5 min after administration of epinephrine [9].

The mean peak plasma epinephrine value in 15 patients with cardiac arrest, before epinephrine therapy, was 10.3 ± 2.9 ng/ml (norepinephrine 7.37 ± 1.8 ng/ml), and after epinephrine therapy 72 ± 31 ng/ml (norepinephrine 22.3 ± 11 ng/ml) [3].

During cardiopulmonary resuscitation in 32 patients, the highest arterial plasma epinephrine level after multiple 1 mg doses was 152 ± 162 ng/ml, and after a high dose (0.2 mg/kg), 393 ± 289 ng/ml [9].

Passage of blood brain barrier: limited.

Elimination half-life: for both epinephrine and norepinephrine approximately 1 minute [2].

Metabolism and excretion

Epinephrine is metabolized by monoamine oxidase to 3,4-dihydroxyphenylglycol aldehyde and then either reduced to 3,4-dihydroxyphenylethylene glycol or oxidized to 3,4-dihydroxymandelic acid. These last named metabolites are converted to glycol and *O*-methylated amines, including catecholamine, which may be conjugated to the corresponding sulfates or glucuronides. Alternatively, epinephrine can initially be methylated by catechol-*O*-methyltransferase to normetanephrine and metanephrine. [5].

Epinephrine itself is a metabolite of *norepinephrine*, also called noradrenaline, which is a catecholamine with chemical formula $C_8H_{11}NO_3$. It is released from the adrenal glands as a hormone into the blood. It is also a neurotransmitter in the nervous system where it is released from noradrenergic neurons during synaptic transmission. Norepinephrine can be methylated by phenylethanolamine N-methyltransferase to epinephrine [10].

Excretion: 60-70% is excreted in the urine within 72 h [1]. About 32% of epinephrine is removed by liver [8].

Pharmacological mechanisms

Epinephrine is a sympathomimetic drug (stimulates the sympathetic nervous system) which action is mediated through adrenergic receptors. It is adrenergic receptor agonist. It binds to α_1 receptors of liver cells, which activate inositol-phospholipid signaling pathway, signaling the phosphorylation of insulin, leading to reduced ability of insulin to bind to its receptors.

Epinephrine also activates β -adrenergic receptors, such as β_1 of the heart, leading to increased cardiac contraction; and β_2 of the liver and muscle cells, thereby activating the adenylate cyclase signaling pathway. Specifically, β_2 receptors exist on many blood vessels. Activation of the adenylate cyclase pathway on this tissue causes inhibition of myosin light chain kinase which, in turn, relaxes the smooth muscle cells of the blood vessel walls causing vasodilation (blood vessels in the body become wider following the relaxation of the smooth muscles in the vessels) and hypotension [10].

Epinephrine in physiologic doses shortens the effective refractory period of the atrium, atrioventricular node and ventricle, improves atrioventricular node conduction and may facilitate the induction of sustained ventricular tachycardia (reviewed in [1]).

Toxicological mechanisms

Epinephrine exerts its effects by interacting with alpha- and beta-adrenergic receptors. Toxicity of epinephrine in overdose is associated with producing of so called “beta-adrenergic syndrome”. Heart rate and cardiac contraction are increased because of β_1 -receptor stimulation, which may lead to myocardial infarction, cardiac arrest, and/or to potentially lethal arrhythmia [2, 5].

Target organs: sympathetic nervous system, heart.

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