SL Pharmacology And Toxicology

Special Issue Article "Adrenergic Drugs" Research Article

Adrenergic Drugs used in Emergency Department

Bedriye Müge Sönmez*

Diskapi Yildirim Beyazit Training and Research Hospital, Department of Emergency Medicine, Turkey

ARTICLE INFO

Received Date: May 12, 2021
Accepted Date: August 20, 2021
Published Date: August 24, 2021

KEYWORDS

Sympathomimetic toxicity
Sympathetic nervous system
Chronotropy
Dromotropy
Inotropy

Copyright: © 2021 Bedriye Müge Sönmez, SL Pharmacology And Toxicology. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Citation for this article: Bedriye Müge Sönmez. Adrenergic Drugs used in Emergency Department. SL Pharmacology And Toxicology. 2021; 3(1):118

Corresponding author:
Bedriye Müge Sönmez,
Diskapi Yildirim Beyazit Training and Research Hospital, Department of Emergency Medicine, Turkey,
Email: mugesonmez06@yahoo.com

ABSTRACT

Adrenergic drugs which bind to adrenergic receptors (α1, α2, β1, β2, β3) act as endogenous catecholamines secreted by the adrenal gland which constitute a "fight or flight" response and are considered the first option in multiple life-threatening conditions. That is to say, these drugs are the mainstay of therapeutic algorithms in Emergency Department (ED). In this review, we aim to list the indications of adrenergic drugs and discuss the clinical evaluation and treatment of sympathomimetic toxicity in ED.

INTRODUCTION

Adrenergic drugs include a large variety of medications that exert a number of physiological actions by binding to adrenergic receptors including alpha-1, alpha-2, beta-1, beta-2, and beta-3 receptors[1]. They are capable of stimulation of Sympathetic Nervous System (SNS), a part of the autonomic nervous system, is responsible for body reactions to stressors or emergency conditions in the form of the "fight or flight" response via circulating compounds such as Nor-Adrenaline (NA) and adrenaline (Ad) and sympathomimetics are considered the first option in multiple life-threatening conditions such as cardiac arrest, shock, asthma attack, or allergic reaction. [2]. This review aims to list the indications of adrenergic drugs and discuss the clinical evaluation and treatment of sympathomimetic toxicity in the Emergency Department (ED).

MECHANISM OF ACTION

Adrenergic receptors are also known as adreno-receptors, which are membrane-bound receptors found in both neuronal and non-neuronal tissues. All of these receptors are G-protein-Coupled Receptors (GPCRs)which are the largest family of membrane proteins that stimulate a number of cellular mechanismsand are dividedinto five families depending on their sequence and structural similarity, basicly (rhodopsin (family A), secretin (family B), glutamate (family C),adhesion and Frizzled/Taste2) [3]. Sympathetic neurons and target myocytes with adrenergic receptor locationsare demonstrated in Figure 1 and Table 1. Most cellular responses to hormones and neurotransmitters, are via the pathways explained below:

1. Alpha-1 Receptor: Mostly postsynaptic this receptor activates phospholipase C, which induces inositol triphosphate (IP3) and diacylglycerol (DAG). These reactions increase intracellular calcium content.

2. Alpha-2 Receptor: Presinaptic this receptor reduces the intracellular cyclic adenosine monophosphate (cAMP) content by inactivating adenylate cyclase.

3. Beta-1 Receptor: Mainly postsynaptic this receptor increases cAMP by activating adenylate cyclase.

4. Beta-2 Receptor: İt is mainly presynaptic and increases cAMP by activating the adenylate cycle via Gs-protein-coupled receptors and decreases cAMP by activatingGi protein-coupled receptors [1,4].

5. Beta-3 Receptor: Postsinaptic this receptor is expressed predominantly in fat cells and activation of adenylate cyclase through Gs is the major mechanism of beta-3 adrenoceptor action. Sympathetic neurons and target myocytes of adrenergic system are shown in Figure.

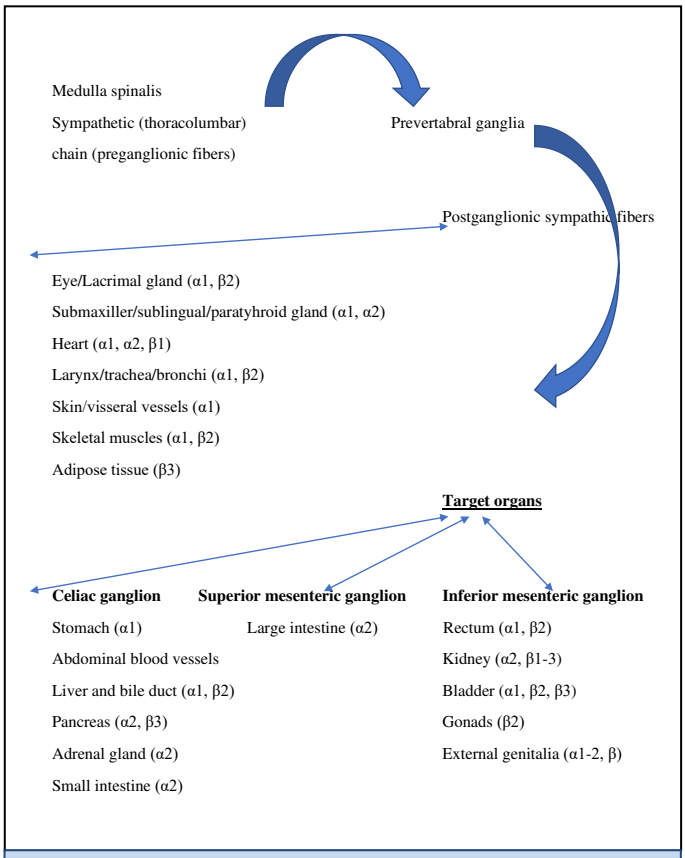

Figure 1: Sympathetic neurons and target myocytes of adrenergic system.

The physiologic functions of adrenoceptors

When activated, α1 receptors cause the contraction of the vascular smooth muscle, radial muscle of the eye and the smooth muscle of the vas deferens; α2 receptors inhibit norepinephrine release from presynaptic neurons, exert sedative effectsvia locus coeruleus, modify pain via dorsal horn, and inhibit insulin release from pancreatic beta cells; β1 receptors augment cardiac output (increased chronotropy, dromotropy, inotropy) and renin release from the kidneys; β2 receptors have relaxation effect on bronchial smooth muscle and vascular smooth muscle (vasodilation); they also inhibit mast cell degranulation and histamine release; β3 receptors inducelipolysis from the adipose tissue [5].

Table: The drugs, adrenergic receptor target(s) and mechanism of action.

Drug	Mechanism of action	Target organ
Adrenaline (epinephrine)	α1 > β	heart, bronchial, arterial and venous system
Noradrenaline	α1-β1 >α2-β2	heart, bronchial, arterial and venous system
Dopamine	α1, β1, β2, Dopaminergic	Heart, arteriel and venous system, renal, brain
Dobutamine	β1 > β2	Heart, vascular system
Phenylephrine	α1	Heart, arterial system
Naphazoline	α1	Eye
Midodrine	α1	Arterial system
Clonidine	α2	Brain, arterial system, eye
Guanfacine	α2	Arterial system
Methyldopa	α2	Arterial system (pregnancy)
Fenoldopam	Dopaminergic	Renal
Lofexidine	α2	CNS
Dexmedetomidine	α	CNS
Salbutamol (albuterol)	β2 >β1	Bronchial and uterin smooth muscle
Terbutaline	β2	Bronchial and uterin smooth muscle
Levalbuterol	β2	Bronchial smooth muscle

Adrenergic drugs used in emergency conditions

Adrenaline (epinephrine): Adrenaline is an endogenous catecholamine that shows agonistic effect on both α1- and β-receptors, with the α1 effect being more potent than the β agonist effect. It is used in ED for the following indications [6];

a) Adult Advanced Cardiac Life Support: The main indication is to treat VF or pulse less VT that cause cardiac arrest and do not respond to the initial shock; it is also used for asystole and pulse less electrical activity (4).

b) Brady dysrhythmias that do not accelerate in response to atropine or transcutaneous pacing.

c) Atraumatic shock episodes (cardiogenic/distributive/septic): Here, it exerts vasopressor and inotropic actionin shock unresponsive to volume infusion or if there is any contraindication to volume infusion (shock) (4).

d) Anaphylaxis and urticaria: (5).

e) Asthma

f) Topical anesthesia

g) Wound management: It exerts vasoconstrictor effect achieving local hemostasis

Noradrenaline (Norepinephrine): Noradrenaline is a sympathomimetic amine synthesized from tyrosine. It has similar structure to adrenaline;however, unlike adrenaline, it carries no methyl group on its nitrogen atom, which makes itbehave

primarily as an alpha1 and beta1 receptor agonist havingvery weak or absent beta2 or alpha2 agonist activity [7]. It is used in ED for the following indications:

a. Atraumatic shock (cardiogenic/distributive/septic): It exerts vasopressor and inotropic action in shock unresponsive to volume infusion or if there is any contraindication to volume infusion (shock); it is the recommended by the sepsis guidelines as the first-line vasopressor for the treatment of severe sepsis or septic shock which remains refractory to sufficient amounts of fluid resuscitation [8],

b. Acute Pulmonary Hypertension: RV function depends on adequate right coronary perfusion, which is augmented by noradrenaline, by increasing aortic root pressure above pulmonary artery pressure [9].

c. Hepatic failure: It is the first-line recommended agent in hepatic failure unresponsive to volume expansion [10].

d. Drug Overdose: It is used to treat central nervous system antidepressant, lithium, β blocker, calcium canal blocker, sympatholytic, pesticide, arsenic, mushroom intoxications associated with profound hypotension refractory to fluid administration and sodium bicarbonate [11].

e. Symptomatic Diabetic Autonomic Neuropathy [12].

f. Adrenal crisis [13].

Dopamine: It is an endogenous catecholamine and a metabolic parent chemical of norepinephrine and epinephrine. It stimulates dopaminergic, α1-, β1-, and β2-receptors in varying doses. Low dose dopamine (0.5 to 2 micrograms/kg/min) causes vasodilation by relaxing vascular smooth muscle of various tissues including kidneys, with the net result of increased urine output. At moderate doses (2 to 10 micrograms/kg/min) it acts on myocardial β1 receptors, leading to increased inotropy and dromotrophy, hence increasing cardiac output. At high dose it acts as a vasoconstrictor, increasing blood pressure and impairing peripheral circulation, through adrenergic receptors alpha-1, beta-1, beta-2, and fields of usage in ED are [14-16];

a. Hemodynamic and cardiac support: Dopamine is primarily used as a vasopressor or inotropic agent for hemodynamic compromise due to profound hypotension resulting from myocardial infarction, trauma, heart failure, renal failure, drug intoxications (lithium, β blocker, calcium canal blocker, sympatholytics, arsenic), and heat stroke when fluid resuscitation is either insufficient to reverse hypotension or contraindicated [17]. Its use as vasopressor is reserved only for a small proportion of patients who are low-risk for developing tachydysrhythmias or bradyarrhythmias [8].

b. Treatment of brady dysrhythmias unresponsive to atropine or transcutaneous pacing

c. Treatment of pulmonary edema caused by acute aortic regurgitation.

d. Treatment of Left Ventricular Assist Device (LVAD) malfunction associated with hemodynamicinstability.

e. Treatment of parkinsonism-hyperpyrexia syndrome: A serious complication of Parkinson disease secondary to sudden dopamine withdrawal [18].

f. Treatment of neuroleptic malignant syndrome: used to mitigate muscle rigidity and fever [19].

Dobutamine: It exerts somemyocardial inotropic effects via beta-1 receptors; it also possesses mild beta-2 agonistic activity lowering systemic vascular resistance, as well as an even lower alpha-1 activity causing vasoconstriction that is largely cancelled by baroreceptor response and beta-2 agonism [20-23].

a. Treatment of decompensated congestive heart failure: Thanks to its sympathomimetic actions, it is of use in cardiogenic shock where it augments stroke volume by increasing inotropy and lowering left ventricular end-systolic volume. The net result is an increased cardiac output.

b. Treatment of pulmonary edema caused by acute mitral and aortic regurgitation.

c. Treatment of LVAD dysfunction.

d. Treatment of pulmonary hypertension associated with right ventricular dysfunction.

Phenylephrine: It is a direct-acting sympathomimetic amine that activates alpha-1 adrenergic receptors, causing venous and arterial vasoconstriction and increased cardiac preload, while having minimal or no beta-adrenergic activity; hence, it is the preferred agent when there is a need for increasing mean arterial pressure without affecting myocardium. Its main areas of usage are [24-26]:

a. Treatment of a traumatic shock: with the exception of septic shock.

b. Treatment of anaphylaxis: In the context of serious epinephrine-induced arrhythmias or tachycardia.

c. During the procedure of nasal intubation using flexible fiberoptic laryngoscopy, nasogastric tube insertion or nasal foreign body removal.: its topical vasoconstrictor effects are used.

d. Treatment of cardiogenic shock caused by hypertrophic obstructive cardiomyopathy.

e. Treatment of persistent priapism.

f. Treatment of epistaxis.

g. During fundoscopic examination for mydriasis.

Naphazoline: An α1 agonist causing vasoconstriction, which is particularly useful for ocular emergencies presenting to ED [27].

Midodrine: An α1 agonist that is useful for the treatment of symptomatic orthostatic hypotension [28].

Clonidine: A centrally acting imidazoline derivative that shows alpha-2 adrenergic agonist action [29]. Its main areas of usage are:

a. Treatment of hypertensive emergencies.

b. Treatment of tetanus by lowering sympathetic drive to control autonomic dysfunction [30].

c. Treatment of opioid withdrawal [31].

d. Treatment of acute angle-closure glaucoma crisis [32].

Guanfacine: A centrally acting alpha-2 adrenergic agonist that mainly finds usage in the treatment of hypertensive emergencies [33].

Methyldopa: This agent is an alpha-2 agonist that is converted to methyl norepinephrine in the Central Nervous System (CNS) and reduces the adrenergic output of the CNS. The net result isa lowered total peripheral resistance and systemic blood pressure but no effects on cardiac output or blood flow to kidneys [34]. Its main area of usage is hypertensive emergencies, particularly during pregnancy [35].

Fenoldopam: This is a unique agonist of dopaminergic (D1) receptors which, unlike other antihypertensive agents, lowers peripheral vascular resistance universally but mainly in renal capillaries, augmenting renal blood flow with resulting natriuresis and diuresis. It is the agent of choice in acute renal failure-induced hypertensive emergencies [36].

Lofexidine: An alpha-2 adrenergic agonist which is mainly used for alleviating symptoms of opioid withdrawal [33].

Dexmedetomidine: A centrally acting alpha agonist that blocks alpha receptors in the brainstem to inhibit norepinephrine release, inhibiting central sympathetic outflow. By these actions, it shows sedative, anxiolytic, hypnotic, analgesic, and sympatholytic effects [37]. The main ED usage is to establish procedural sedation; additionally, it is the treatment of choice for the management of delirium associated with alcohol withdrawal [38].

Salbutamol (albuterol): This is abeta-2 adrenergic receptor stimulant. Itcauses relaxation of the smooth muscle in bronchial walls and prevents the cells, particularly mast cells, from releasing mediators of immediate hypersensitivity; it is also a weak β1 agonist [39]. Its main indications are:

a. Mitigation of bronchospasm secondary to anaphylaxis and allergic reactions.

b. Urgent reduction of blood potassium level in severe hyperkalemia.

c. Treatment of acute asthma, acute exacerbations of chronic obstructive pulmonary disease, high-altitude bronchitis and mushroom poisoning, by reducing pulmonary secretions and bronchospasm.

d. Treatment of premature contractions in pregnancy.

Terbutaline: Abeta-2 selective adrenergic agonist (SABA) with a short duration of action. It causes relaxation of smooth muscle on bronchial and uterine walls [40]. Its main indications include:

a. Treatment of acute asthma, regardless of pregnancy status; acute exacerbations of chronic obstructive pulmonary disease

b. Emergency treatment of hyperkalemia if albuterol cannot be administered.

c. As a tocolytic used to arrest labor contractions [41].

Levalbuterol: A relatively selective SABA that is mainly used to treat acute asthma, status asthmaticus, and acute exacerbations of chronic obstructive pulmonary disease [40].

Sympathomimetic intoxication in ED

Sympathomimetic drugs act similarly with endogenous neurotransmitters in that they activate the sympathetic nervous system; net clinical effects depend on the activated adrenergic receptors (a1, a2, b1, b2),some of which are stimulating and others inhibitory [42,43]. Amphetamine, phenylpropanolamine, ephedrine, cocaine are some sympathomimetic drugs. Their clinical signs of intoxication are very diverse and include cardiovascular (dysrhythmias, myocarditis, cardiomyopathy (including takotsubo cardiomyopathy), acute coronary syndromes, aortic rupture, aortic and coronary artery

dissection), central nervous system (seizures, cerebral and spinal cord infarctions, hemorrhages, cerebral vasculitis, intracranial abscesses, choreoathetosis, repetitive movements and acute dystonic reactions associated with dopamine dysregulation, central retinal artery occlusion, and bilateral blindness, cocaine washout syndrome), pulmonary (pulmonary hemorrhage, pneumomediastinum, pneumothorax, and pneumopericardium due to barotrauma, pneumonitis, asthma, pulmonary edema, lung injury), gastrointestinal (intestinal ischemia, bowel necrosis, ischemic colitis, splenic infarctions, GI ulceration, hemorrhage, and perforation), endocrinological (hyponatremia), and renal (traumatic and nontraumatic rhabdomyolysis, acute kidney failure, renal infarction) manifestations [44].

Sympathomimetic poisoning is treated with benzodiazepines to achieve sedation and to stop seizures, as well as aspirin, nitroglycerin, and additional therapies against acute coronary syndromes as dictated by the electrocardiograph. If there is true or suspected acute coronary syndrome, the aim is to treat dysrhythmias, to lower sedative-resistant high blood pressure using phentolamine, nitroglycerin, nicardipine, or intravenous sodium nitroprusside infusion, to lower body temperature by aggressive cooling, to reverse renal effects of rhabdomyolysis by administering intravenous fluids, and to apply supportive measures [45].

CONCLUSIONS

The emergency physician should know how to quickly select the right drug for the right patient in an unstabil emergency department.

REFERENCES

1. Khashayar Farzam, Ariel Kidron, Anand D Lakhkar. (2021). Adrenergic Drugs.
2. Paravati S, Rosani A, Warrington SJ. (2021). Physiology, Catecholamines, in StatPearls. Treasure Island (FL).
3. Rosenbaum DM, Rasmussen SG, Kobilka BK. (2009). The structure and function of G-protein-coupled receptors. Nature. 459: 356-363.
4. Michel MC, Bond RA, Summers RJ. (2019). Adrenoceptors-New roles for old players. Br J Pharmacol. 176: 2339-2342.
5. Bylund DB. (2013). Adrenergic Receptors. Encyclopedia of Biological Chemistry. 57-60.
6. Dalal R, Grujic D. (2021). Epinephrine, in StatPearls. Treasure Island (FL).
7. Smith MD, Maani CV. (2021). Norepinephrine, in StatPearls. Treasure Island (FL).
8. Lat I, Coopersmith CM, Daniel De Backer, Craig M Coopersmith. (2021) for the Research Committee of the Surviving Sepsis Campaign. The surviving sepsis campaign: fluid resuscitation and vasopressor therapy research priorities in adult patients. Intensive Care Med Exp. 9: 10.
9. Kwak YL, Lee CS, Park YH, Hong YW. (2002). The effect of phenylephrine and norepinephrine in patients with chronic pulmonary hypertension*. Anaesthesia, 57: 9-14.
10. Satsangi S. (2018). Noradrenaline for Hepatorenal Syndrome in Patients With Acute on Chronic Liver Failure: Hope Remains! Hepatology. 68: 2443-2444.
11. Eyer F. (2013). Hypotension and Shock in the Poisoned Patient. Critical Care Toxicology. 1-30.
12. Gabriella Deli, Edit Bosnyak, Gabriella Pusch, Samuel Komoly, Gergely Feher. (2013). Diabetic Neuropathies: Diagnosis and Management. Neuroendocrinology. 98: 267-280.
13. Elshimy G, Chippa V, Jeong JM. (2021). Adrenal Crisis, in StatPearls. Treasure Island (FL).
14. Sonne J, Goyal A, Bansal P, Lopez-Ojeda W. (2021). Dopamine, in StatPearls. Treasure Island (FL).
15. Jasmeet Soar, Katherine M. Berg, Lars W. Andersen, Bernd W. Böttiger, Sofia Cacciola, et al. (2020). Adult Advanced Life Support: 2020 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. Resuscitation. 156: A80-A119.
16. Evgenij V Potapov, Christiaan Antonides, Maria G Crespo-Leiro, Alain Combes, Gloria Färber, et al. (2019). 2019 EACTS Expert Consensus on long-term mechanical circulatory support. Eur J Cardiothorac Surg. 56: 230-270.
17. Bellomo R, Cole L, Ronco C. (1998). Hemodynamic support and the role of dopamine. Kidney Int Suppl. 66: S71-74.
18. Newman EJ, Grosset DG, Kennedy PG. (2009). The parkinsonism-hyperpyrexia syndrome. Neurocrit Care. 10: 136-140.
19. Simon LV, Hashmi MF, Callahan AL. (2021). Neuroleptic Malignant Syndrome, in StatPearls. Treasure Island (FL).

20. Ashkar H, Makaryus AN. (2001). Dobutamine, in StatPearls. Treasure Island (FL).
21. Stout KK, Verrier ED. (2009). Acute Valvular Regurgitation. Circulation. 119: 3232-3241.
22. Tsapenko MV, Arseniy V Tsapenko, Thomas Bo Comfere, Girish K Mour, Sunil V Mankad, et al. (2008). Arterial pulmonary hypertension in noncardiac intensive care unit. Vasc Health Risk Manag. 4: 1043-1060.
23. Mateja K. Jezovnik, Igor D. Gregoric, Pavel Poredos. (2017). Medical complications in patients with LVAD devices. e-Journal of Cardiology Practice. 14.
24. Richards E, Lopez MJ, Maani CV. (2021). Phenylephrine, in StatPearls. Treasure Island (FL).
25. Namali Corea. (2007). Phenylephrine. xPharm: The Comprehensive Pharmacology Reference. 1-5.
26. Patil PM, Anand R. (2011). Nasal foreign bodies: a review of management strategies and a clinical scenario presentation. Craniomaxillofac Trauma Reconstr. 4: 53-58.
27. Kuzminov B, Turkina V, Kuzminov Y. (2018). Rationale for naphazoline effects in-depth study. Current Issues in Pharmacy and Medical Sciences. 31: 29-33.
28. Parsaik AK, Singh B, Altayar O, Mascarenhas SS, Singh SK, et al. (2013). Midodrine for orthostatic hypotension: a systematic review and meta-analysis of clinical trials. J Gen Intern Med. 28: 1496-1503.
29. Yasaei R, Saadabadi A. (2021). Clonidine, in StatPearls. Treasure Island (FL).
30. T van den Heever, M G L Spruyt. (2017). The treatment of autonomic dysfunction in tetanus. Southern African Journal of Critical Care. 33: 28-31.
31. (2009). Clinical Guidelines for Withdrawal Management and Treatment of Drug Dependence in Closed Settings. Geneva.
32. Ah-Kee EY, Egong E, Shafi A, Lim LT, Yimet JL. (2015). A review of drug-induced acute angle closure glaucoma for non-ophthalmologists. Qatar Med J. 2015: 6.
33. Taylor BN, Cassagnol M. (2021). Alpha Adrenergic Receptors, in StatPearls. Treasure Island (FL).
34. Gupta M, Al Khalili Y. (2021). Methyldopa, in StatPearls. Treasure Island (FL).
35. Hoeltzenbein M, Beck E, Fietz AK, Wernicke J, Zinke S, et al. (2017). Pregnancy Outcome After First Trimester Use of Methyldopa A Prospective Cohort Study. Hypertension. 70: 201-208.
36. Szymanski MW, Richards JR. (2021). Fenoldopam, in StatPearls. Treasure Island (FL).
37. Reel B, Maani CV. (2021). Dexmedetomidine, in StatPearls. Treasure Island (FL).
38. Beg M, Fisher S, Siu D, Rajan S, Troxell L, et al. (2016). Treatment of Alcohol Withdrawal Syndrome with and without Dexmedetomidine. Perm J. Spring. 20: 49–53.
39. Johnson DB, Merrell BJ, Bounds CG. (2021). Albuterol, in StatPearls. Treasure Island (FL).
40. Hsu E, Bajaj T. (2021). Beta 2 Agonists, in StatPearls. Treasure Island (FL).
41. Motazedian S, Ghaffarpasand F, Mojtahedi K, Asadiet N, et al. (2010). Terbutaline versus salbutamol for suppression of preterm labor: a randomized clinical trial. Ann Saudi Med. 30: 370-375.
42. Williams RH, Erickson T, Broussard LA. (2000). Evaluating sympathomimetic intoxication in an emergency setting. Laboratory Medicine. 31: 497-507.
43. Holstege CP, Borek HA. (2012). Toxidromes. Critical Care Clinics. 28: 479-498.
44. Wightman RS, P.J. (2020). Tintinalli's Emergency Medicine A Comprehensive Study Guide. 9th edn. Cocaine and Amphetamines.
45. Goldstein S, Richards JR. (2021). Sympathomimetic Toxicity, in StatPearls. Treasure Island (FL).