Chapter 16
Peripheral Vasodilators

Ratan K. Banik and Jay S. Berger

Contents

> We were looking for a drug that would dilate coronary arteries. More blood, more oxygen, less angina—better lifestyle. …..we were doing clinical tests in V.A. hospital.....And we found we couldn't get the pills back from the vets. Then doctors started finding pills missing from the hospital cabinets. Very quickly we learned the reason. The drug is now known as Viagra, or "the little blue pill," and is prescribed for impotence. -James R. Gardner, Ph.D., Vice President, Pfizer Inc. [1]

Vasodilators, as their name imply, treat hypertension by causing the smooth muscle walls of blood vessels to relax, thus dilating the vessel. The systemic peripheral vascular resistance (afterload) is reduced by dilating on the arterial side of the

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Table 16.1 Principles of vasodilator therapy

Preload reduction	Afterload reduction
Decreased pulmonary venous congestion	Reduction in ventricular wall stress
Decreased ventricular wall stress	Increased coronary blood flow
Increased coronary blood flow	Enhanced oxygen delivery
Improved myocardial oxygen delivery	Improved systolic contractile function
	Reduction in mitral regurgitation

Vasodilators work by reducing preload, afterload, or both preload and afterload. Preload reduction results in decreased intraventricular pressures and improved myocardial oxygen delivery. Afterload reduction results in decreased work for the heart which improves hemodynamics in patients with heart failure

Table 16.2 Classification of systemic vasodilators

Therapeutic objective	Medication
Arterial vasodilation (Decreased afterload)	Hydralazine Fenoldopam
Venous vasodilation (Decreased preload)	Nitroglycerin
Mixed (Decreased afterload and preload)	Nitroprusside ARBs (e.g., losartan) ACEI (e.g., enalapril)

ARB angiotensin receptor blocker, *ACEI* angiotensin-converting enzyme inhibitors

vascular system. The peripheral venous return (preload) is reduced by dilating the veins. The overall effect is a decrease in arterial blood pressure, an increase in ventricular output, and a decrease in end-diastolic volume (Table 16.1). In hypovolemic states, vasodilators must be used with caution because they can worsen perfusion to vital organs. Most vasodilating medications to some degree work on both the arterial side and the venous side of the vascular system. However, some vasodilators work more specifically on one side or the other (Table 16.2). These medications are used in a wide variety of disease states, such as coronary artery disease, heart failure, and hypertension. The effectiveness of vasodilator treatment for patients with chronic congestive heart failure has been demonstrated in large multicenter clinical trials (Vasodilator-Heart Failure Trial I and II) [2–4]. The combination of different vasodilators has been shown to significantly improve symptoms, exercise tolerance, and survival of heart failure patients.

Nitroglycerin

Class: Antianginal Agent, Nitrate, Vasodilator

Nitroglycerin is originally discovered in 1847 by Swedish Scientist Dr. Sobrero by interacting glycerol, nitric acid, and sulfuric acid. Originally discovered as an explosive, nitroglycerin was quickly shown to relieve the chest pain associated with

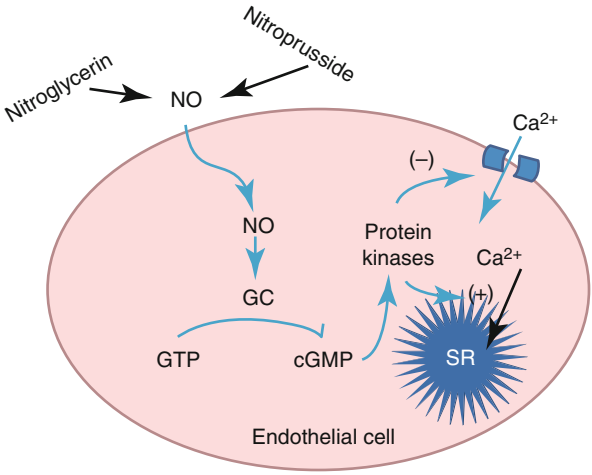


Fig. 16.1 Mechanism of action of nitric oxide (*NO*) induced vasodilation. NO activates the cytosolic guanylate cyclase, to form cyclic guanosine monophosphate, which in turn activates protein kinases. These kinases block calcium entry inside the cell and enhance migration of calcium to intracellular stores resulting in vasodilation. *NO* nitric oxide, *GC* guanylyl cyclase, *cGMP* cyclic GMP

angina pectoris. The exact mechanism for the pain relief remained a mystery for greater than 100 years. It is now known that nitroglycerin releases nitric oxide from vascular smooth muscle cells, which initiates a cascade of events that results in venous relaxation. The investigator Ferid Murad won the Nobel Prize in 1998 for his discovery (along with Robert F. Furchgott, Louis J. Ignarro) [5].

Mechanism of Action

Nitroglycerin binds to the surface of endothelial cells and acts as substrate for formation of nitric oxide (NO). The nitric oxide then moves out of the endothelial cells and binds with its receptor on smooth muscle cell (Fig. 16.1). Once inside the smooth muscle cells, NO converts guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). The cGMP reduces cytosolic calcium levels by two mechanisms: First, cGMP-dependent protein kinase G is activated which prevents calcium entry into the cell. Second, mitochondrial uptake of calcium is simulated. The overall effect is decreased intracellular calcium levels resulting in smooth muscle cell relaxation [5].

Indications

The primary indication of nitroglycerin is the treatment and prevention of acute chest pain associated with angina pectoris. Acute onset of chest pain can be treated with quickly dissolving sublingual tablets (0.3–0.6 mg) or oral spray (0.4–0.8 mg) administered every 5 min until pain is relieved up to three doses within 15 min [6]. Prevention of pain can be achieved with quickly acting sublingual tablets (0.3–0.6 mg) or oral spray (0.4–0.8 mg) just prior to activity, or extended release tablets (isosorbide-5-mononitrate). The IV form of nitroglycerin is indicated for persistent unstable angina that is poorly responsive to oral form, congestive heart failure with

acute MI, hypertensive emergency with acute pulmonary edema, and induction of intraoperative hypotension. Start 10–20 mcg/min and titrate up by 5–10 mcg/min every 5–10 min until desired effect. The maximum dose is 500 mcg/min [7]. Not recommended in pediatrics. Pregnancy safety: Category C, not known if it is secreted in breast milk.

Drug Interactions and Contraindications

Nitroglycerin decreases the anticoagulation effect of heparin, increases the paralytic effect of pancuronium, and potentiates the vasodilatory effect of phosphodiesterase inhibitors which can result in vasodilatory shock. Patients taking ASA >500 mg may have decreased metabolism of nitroglycerin. Nitroglycerin is contraindicated in hypersensitivity to nitrates, glaucoma and hypovolemia, head trauma, constrictive pericarditis, and cardiac tamponade.

Side Effects

The most common side effect is headache, which can be persistent and severe due to dilation of cerebral blood vessels. Other side effects include postural hypotension, tachycardia, syncope, palpitation, anxiety, dizziness, vertigo, anxiety, and weakness. Most of these side effects are related to excessive vasodilation.

Clinical Pearls

I. Nitroglycerine is the first-line treatment of acute chest pain.
II. Must use nonabsorbable infusion set because of absorption of the nitroglycerine by standard PVC tubing.
III. Warn patients about the most common side effects of nitroglycerine: headache, orthostatic hypotension, and dry mouth.
IV. Administration of IV nitroglycerine requires continuous hemodynamic monitoring.
V. Administration of nitroglycerine with other vasodilators can precipitate a shock state.

Nitroprusside (SNP)

Class: Antihypertensive, Nitrate, Vasodilator

The first recorded use of sodium nitroprusside (SNP) in humans was in 1928; however, FDA approval was delayed until 1974, because of safety concern over cyanide toxicity. SNP is a rapidly acting (<30 s) powerful vasodilator, which affects both

arterial and venous smooth muscle cells. In addition to its quick onset, the vasodilatory effect of SNP ceases within 1–3 min of discontinuing the infusion.

Mechanism of Action

Sodium nitroprusside is comprised of five cyanide moieties and one nitrosyl group. Once infused, it converts oxyhemoglobin (Fe^{++}) to methemoglobin (Fe^{+++}) and releases cyanide and NO moieties. Unlike nitroglycerin, SNP directly generates NO, which relaxes vascular smooth muscle by a similar mechanism described above. The cyanide moiety is converted to thiocyanate by thiosulfate sulfurtransferase within the liver. The conversion of cyanide to thiocyanate utilizes sulfur stores. Depletion of sulfur stores by malnutrition or in postoperative patients facilitates accumulation of cyanides and increases the risk of developing cyanide toxicity. The metabolite thiocyanate is excreted in the urine [8].

Indications

The rapid onset of action makes SNP ideal for the treatment of hypertensive crisis. The short duration of action allows SNP to be utilized for deliberate hypotension in a variety of surgical procedures, such as major spinal surgery.

Dosing Options

The only route of administration of SNP is via an intravenous infusion. The dosing for pediatrics and adults is the same. The initial infusion rate is started low at 0.3 g/kg/min and is titrated up every few minutes to a maximum does of 10 g/kg/min [9]. It is not indicated in patients with renal impairment (creatinine clearance <10 ml/min). The use of higher doses limited to a maximum duration of 10 min. Nitroprusside should not be given to pregnant women. It is not known if SNP and its metabolites are excreted in human milk [6].

Drug Interactions and Contraindications

The most common side effects are hypotension, palpitations, restlessness, retching, retrosternal discomfort, and muscle twitching which are related to rapid reduction of blood pressure and disappear once infusion is discontinued. Less commonly seen are the following: significant methemoglobinemia whose incidence increases when the maximum recommended dose of 10 g/kg/min is infused for more than 16 h and when medications such as benzocaine and lidocaine that cause methemoglobinemia are concurrently administered. The administration of >2 mcg/kg/min in patients with renal insufficiency or administration at the maximum dose for greater than 24 h can increase the risk of cyanide toxicity [9]. The signs and symptoms of cyanide

toxicity (>5 mg/dl) include metabolic acidosis, nausea, mental confusion, and muscle weakness. The degree of pulmonary shunting can also increase due to SNP attenuating the normal physiologic response of pulmonary artery constriction to hypoxia.

Clinical Pearls

I. Methemoglobinemia should be suspected in patients exhibiting low oxygen saturation (~85 %) despite adequate cardiac output and PO_2. Pay attention at chocolate color blood while taking ABG sample [8].
II. Cyanide toxicity is a clinical diagnosis because cyanide level assay is technically difficult to perform and metabolic acidosis is a lagging indicator. In an awake, spontaneously breathing patient, their breath will smell like almonds and the patient will suddenly become confused. Suspicion should be high when the drug's hypotensive effect is gone despite increased infusion rates. Treatment should include stopping the infusion, mechanical ventilation with 100 % oxygen, and administering sodium thiosulfate (150 mg/kg over 15 min) or 3 % sodium nitrate (5 mg/kg over 5 min) [10].
III. If blood pressure is not controlled by the maximum rate after 10 min, check acid-base balance and venous oxygen concentration for evidence of cyanide toxicity; however, these indicators are not reliable.
IV. Nitroprusside administration is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency because these patients are unable to clear methemoglobin [11].

Hydralazine

Class: Antihypertensive, Arterial Vasodilator

Hydralazine is a direct arteriolar vasodilator with almost no effect on the venous circulation. It was discovered in 1950 by Franz Gross. The increase in renal blood flow despite the fall in blood pressure has been considered a unique feature of this drug [12].

Mechanism of Action

Hydralazine reduces afterload by causing arterial vasodilation. The decrease in diastolic blood pressure is greater than the decrease in the systolic blood pressure. Some studies suggest that potassium channels are opened for prolonged period causing hyperpolarization of the smooth muscle cells. Another proposed mechanism involves the production of NO stimulating cGMP as described previously [13]. Lastly, hydralazine has been shown to interfere with the release of calcium from the endoplasmic reticulum which inhibits vasoconstriction.

Indications

Hydralazine specifically dilates arteries which minimizes orthostatic hypotension that is associated with other vasodilators. Renal flow is usually maintained or slightly increased by hydralazine making it an ideal medication to use in patients with renal disease; however, clearance is dependent on renal function. Similarly, hydralazine is a first-line medication for the treatment of preeclampsia because it slightly increases uteroplacental blood flow. The reduction of afterload by this drug is beneficial for treatment of congestive heart failure when conventional therapy fails.

Dosing Options

The oral dose is 10–50 mg every 6 h. The IV/IM dose is 5–20 mg every 4 h. Blood pressure starts to decrease within 10–30 min of administration. Pediatric dose is 0.2–0.5 mg/kg IV every 4–6 h [6].

Drug Interactions and Contraindications

The arterial vasodilation causes an increase in cerebral blood flow which contraindicates its use in patients with increased intracranial pressure. It is also contraindicated in the treatment of aortic dissection because the reflex tachycardia may propagate the dissection. Similarly, the reflex tachycardia increases the work of the heart and contraindicates its use in patients with underlying coronary artery disease.

Side Effects

Arterial vasodilation by hydralazine causes stimulation of the sympathetic nervous system which causes tachycardia, myocardial contractility, and increase plasma renin activity. Increased plasma renin stimulates aldosterone resulting in fluid and water retention. Side effects include fluid retention, tachycardia, palpitations, headache, lupus-like syndrome, and neonatal thrombocytopenia.

Clinical Pearls

I. The reflex tachycardia can be prevented by the administration of a low-dose beta-blocker.
II. Genetic variations in the liver enzyme N-acetyltransferase expression determine the hypotensive effect of hydralazine. High levels of enzyme expression result in less vasodilatory effect [14].

III. Lupus can occur in as many as 10 % of patients and presents as joint pain, fever, and anemia. Seventy-three percent of patients experiencing hydralazine-induced lupus are HLA-DRw4 positive [14].
IV. Chronic (>3 months) use of hydralazine can cause peripheral neuropathy by inhibiting the enzymes involved in pyridoxine metabolism. Prophylactic treatment with pyridoxine with oral hydralazine [15].

Calcium Channel Blockers (CCB)

Class: Antihypertensive, Antiarrhythmic, Calcium Channel Blocker, Vasodilator

Calcium channel blockers inhibit the influx of calcium into vascular smooth muscles and cardiac cells. This class of medications is a heterogeneous group with dissimilar structures and function. Dihydropyridines (drug with suffix "dipine," e.g., nifedipine, amlodipine, and nicardipine) cause arterial vasodilation, and non-dihydropyridines (e.g., verapamil and diltiazem) decrease myocardial contractility and heart rate. Further discussion of non-dihydropyridines is outside the scope of this chapter.

Mechanism of Action

Dihydropyridines inhibit voltage-sensitive L-type calcium channels preventing calcium entry into the smooth muscle cells and thus contraction of these cells.

Indications

The patient's comorbidities play a large role in choices of which calcium channel blocker is administered. Nifedipine and nicardipine are used for isolated hypertension in patients with asthma, diabetes mellitus, or renal dysfunction and in the elderly and African American patients. Nifedipine is useful for the treatment of Prinzmetal's angina. In addition to coronary artery vasodilation, the reduced afterload and left ventricular volume results in decrease in myocardial oxygen demand. Nifedipine has minimal negative inotropic activity, minimal effect on nodal activity, and no antiarrhythmic activity, which therefore causes no electrocardiographic changes. Nimodipine has greater effect on cerebral arteries and is indicated for cerebral spasms after subarachnoid hemorrhage or ruptured intracranial aneurysm [16].

Dosing Options

Nifedipine is available as both a short-acting and an extended release form, which are not FDA approved for pediatric use. The short-acting form is used

to treat acute coronary spasm titrating from low doses of 20–30 mg 3–4 times per day to a maximum dose of 180 mg per day [6]. The extended release form is used to treat chronic coronary spasm and hypertension by starting at 30–60 mg once per day to a maximum of 120 mg per day [6]. Nicardipine is available in an oral form as are all calcium channel blockers; however, it is the only one available in intravenous form. Thus, nicardipine is the only calcium channel blocker that can be utilized to tightly modulate blood pressure. Start the infusion at 2.5 mg/h titrating up every 15 min to a maximum dose of 15 mg/h [6]. Nimodipine is prophylactically administered to prevent cerebral artery spasm after subarachnoid hemorrhage at a dose of 60 mg every 4 h for 21 days [17].

Drug Interactions and Contraindications

The dihydropyridines are potent vasodilators; therefore, they should not be given to patients with aortic stenosis, cardiomyopathy, heart failure, or recent MI.

Side Effects

Short-acting dihydropyridines (e.g., nifedipine) cause rapid onset of vasodilation which is associated with flushing, tachycardia, palpitation, and headache. These side effects are negligible with the extended release preparations. Peripheral edema has an incidence of 7–30 % of patients taking a calcium channel blocker regardless of the preparation used.

Clinical Pearls

I. Calcium entry blockers may augment the effects of both depolarizing and non-depolarizing muscle relaxants [11].
II. Hypotension induced by calcium channel blocker administration is often not responsive to the administration of intravenous calcium; however, it usually responds to direct vasoconstrictors such as phenylephrine.

Angiotensin-Converting Enzyme (ACE) Inhibitors

Class: Antihypertensive, Vasodilator

In the late 1960s, the Nobel Prize winning scientist Sir John Vance observed that the effects of Brazilian viper venom was due to sudden decrease in blood pressure. A potent inhibitor of the angiotensin-converting enzyme (ACE) was isolated in the venom. This inhibitor was used to develop the first synthetic

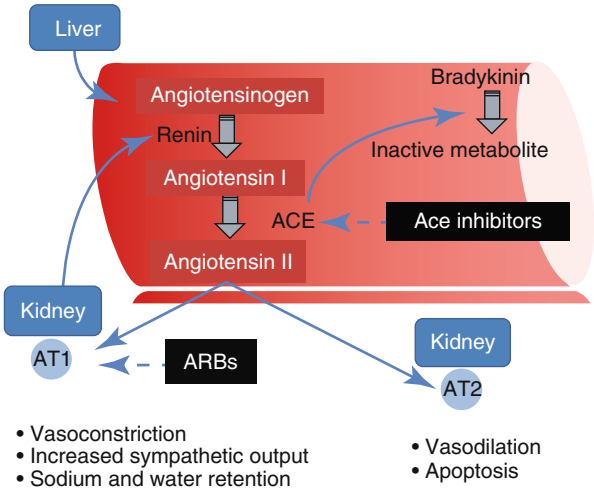


Fig. 16.2 Mechanism of action of angiotensin-converting enzyme (*ACE*) inhibitors and angiotensin receptor blockade. Angiotensinogen is converted to angiotensin I by renin secreted from juxtaglomerular apparatus in the kidney. Angiotensin I is further converted to angiotensin II by ACEIs, which are released in the lungs and also responsible for breakdown of bradykinin, a potent vasodilator. Angiotensin II acts on AT1 receptor in the kidney, which is blocked by ARBs. The role of AT2 receptor in adults remains poorly understood. Note that the production of bradykinin is enhanced by ACE inhibitors (not by ARBs) which is largely responsible for major side effects of these drugs (e.g., dry cough, angioedema)

ACE inhibitor, captopril, for treatment of hypertension. This class of medication is now a mainstay in the treatment of hypertension, heart failure, and chronic kidney disease.

Mechanisms of Action

ACE inhibitors attenuate effects of the renin-angiotensin system (Fig. 16.2). The juxtaglomerular apparatus of the renal cortex secretes renin, which acts on plasma angiotensinogen to form angiotensin I. ACE is then converts angiotensin I to angiotensin II in the lung. Angiotensin II directly constricts vascular smooth muscle cells and stimulates the adrenal gland to release aldosterone and epinephrine. By interfering with the formation of angiotensin II, ACE inhibitors inhibit vasoconstriction [13]. In addition, ACE inhibitors slow the degradation of kinins, which directly cause vasodilation. An elevated level of bradykinin results in an increased conversion of arachidonic acid to prostaglandins, which are also potent vasodilators [13].

Indications

In hypertensive diabetic patients, ACE inhibitors have been shown to delay the progression of diabetic nephropathy. Vasodilation of the afferent arteriole leads to an increase in the renal blood flow; however, vasodilation of the efferent arteriole causes a decrease in the glomerular filtration rate. In heart failure patients, the administration of an ACE inhibitor has been shown in multiple trials to significantly reduce morbidity and mortality. Often an ACE inhibitor is administered in conjunction with a diuretic. The hypovolemia induced by the diuretic triggers vasoconstriction via the angiotensin II system, which is prevented by the ACE inhibitor.

Dosing Options

To avoid hypotension and other adverse side effects, start with a low dose and gradually titrate the dose to the targeted response. Captopril: The starting dose is 6.25–12.5 mg TID and can be titrated up to a maximum dose of 50 mg TID. In pediatrics, the starting dose is 0.15–0.3 mg/kg/day in 3 divided doses and can be titrated up to a maximum dose of 6 mg/kg/day in 3 divided doses. Lisinopril: The starting dose is 2.5 mg per day and may be titrated up to a maximum dose of 40 mg per day. In pediatrics (age >6 years old), the starting dose is 0.07 mg/kg per day and can be titrated up to a maximum dose of 5 mg per day [6].

Contraindications and Drug Interactions

The development of side effects such as a cough or angioedema as described below should prompt the discontinuation of therapy. Bilateral renal artery stenosis is a contraindication to ACE inhibitor administration. Angiotensin II causes vasoconstriction of the efferent arterioles in the glomerulus, increasing the relative glomerular filtration rate. This vasoconstriction is prevented by an ACE inhibitor. The glomerular filtration rate is maintained by vasodilation of the afferent arterioles; however, if bilateral renal artery stenosis exists, the decrease in glomerular filtration rate cannot be compensated for. Pregnancy is also a contraindication to ACE inhibitor administration, which may in the second or third trimester cause pulmonary hypoplasia, intrauterine growth retardation, and oligohydramnios secondary to fetal hypotension [18].

Side Effects

In general, ACE inhibitors are well tolerated and have a low incidence of side effects. Like all vasodilators, ACE inhibitors can cause hypotensive related symptoms such as dizziness and headache. Roughly 20 % of patients will complain of a

dry cough. The etiology of the cough is unclear but may be related to the increased kinin level. Symptoms typically cease after the discontinuation of therapy. Less frequently, patients on ACE inhibitors develop angioedema which depending on severity may necessitate endotracheal intubation. Fortunately most cases resolve spontaneously after discontinuation of the medication. In patients with renal insufficiency, the incidence of hyperkalemia increased by the administration of an ACE inhibitor [11].

Clinical Pearls

I. Patients undergoing general anesthesia are likely to experience post-induction hypotension, which must be anticipated and aggressively treated [19].
II. Angioedema is an infrequent life-threatening complication of ACE inhibitors (incidence approximately 0.1 %). Patients typically present with lip and tongue swelling and possibly laryngeal edema. These patients require close monitoring, and if the airway appears to be at risk, early endotracheal intubation is prudent [19].

Angiotensin Receptor Blockers (ARBs)

Class: Antihypertensive, AT1 Receptor Antagonists, Vasodilator

The disruption of the renin-angiotensin system by ACE inhibitors is an effective means to treat hypertension; however, as mentioned previously ACE inhibitors are associated with some unwanted side effects. ACE inhibitors prevent the formation of angiotensin II. The interaction of angiotensin II with the smooth muscle cells is prohibited by ARBs (Fig. 16.2). In circumstances where the side effects of ACE inhibitors cannot be tolerated, ARBs have been shown to effectively control blood pressure.

Mechanism of Action

The conversion of angiotensin I to angiotensin II is catalyzed by angiotensin-converting enzyme in the lung. Angiotensin II then interacts with the AT1 receptor on smooth muscle cells causing vasoconstriction. This interaction is prevented by ARBs. Unlike ACE inhibitors, ARBs do not interfere with kinin degradation and consequently bradykinin levels do not increase. The difference in mechanism of action may explain the significantly lower incidence of cough associated with ARBs versus ACE inhibitors [13].

Dosing Options

The typical starting dose of losartan is 50 mg per day, but the dose can be reduced to 25 mg per day in hypovolemic patients. The maximum dose is 100 mg per day. Losartan is also marketed as a combination medication with hydrochlorothiazide (HCTZ) that comes in the following concentrations: losartan/HCTZ 50 mg/12.5 mg, 100 mg/12.5 mg, and 100 mg/25 mg. The pediatric dose of losartan is 0.7 mg/kg per day to a maximum dose of 50 mg/day [6].

Indications

ACE inhibitors are superior to ARBs in the treatment of hypertension in patients with heart failure. The difference in their mechanism of action of these two classes of medication may explain the difference in their efficacy. ACE inhibitors result in reduced levels of angiotensin II, which downregulates the activity at both AT1 and AT2 receptors. ARBs only interfere with the interaction between angiotensin II and the AT1 receptor (Fig. 16.2). There is limited evidence regarding the beneficial effects of administering both and ARB and an ACE inhibitor. The combination is, however, contraindicated in post-MI patients. Losartan has been shown to increase uric acid levels, questioning its benefit in patients with hypertension and gout.

Contraindications and Drug Interactions

Fluconazole inhibits metabolism of ARBs, causing an increased antihypertensive effect. Indomethacin, phenobarbital, and rifampin decrease their effectiveness of ARBs. Telmisartan enhances insulin sensitivity, which may help in blood sugar control in diabetic patients. ARBs may increase lithium levels out of the therapeutic levels and into toxic levels. ARBs should be used with caution in patients who have difficulty regulating potassium levels. ARBs are contraindicated in pregnancy and in patients who have angioedema with ACE inhibitors.

Side Effects

ARBs are well tolerated and relatively have a low incidence of side effects. Cough and angioedema may occur; however, the incidence is much less than compared for ACE inhibitors. ARBs are associated with a significantly higher rate of symptomatic hypotension than are ACE inhibitors.

Clinical Pearls

I. The risk of post-induction hypotension is greater in patients who continue to take ARBs up to the day of surgery; nevertheless, studies show that the benefits of blood pressure control outweigh this risk of perioperative hypotension [20].
II. The patients with poorly controlled hypertension should be medically optimized before proceeding to elective surgery. In general, it is recommended that elective surgery should be canceled for patients with blood pressure >170/110 in multiple measurements [20].

Fenoldopam

Class: Antihypertensive, Dopamine Agonist, Vasodilator

Fenoldopam is a selective dopamine-1 receptor agonist which lowers blood pressure by decreasing peripheral vascular resistance, diuresis, and renal vasodilation. The drug is 6–10 times more potent than dopamine in producing renal vasodilatation and has no adrenergic effects.

Mechanism of Action

Stimulation of dopamine DA1 receptor causes systemic arterial vasodilation, specifically in renal, coronary, cerebral, and mesenteric arteries. Generalized arterial vasodilation rapidly reduces peripheral vascular resistance and blood pressure. In the kidney, both the afferent and efferent arterioles are dilated, which results in a large increase in renal blood flow with little effect on the glomerular filtration rate. In addition, it inhibits the Na-K-ATPase pump in the proximal tubular cells and sodium reabsorption in the collecting tubules. The net effect is natriuresis and diuresis.

Indications

The drug is indicated for treatment of severe hypertension and short-term (<4 h) blood pressure reduction in pediatric patients. It may be useful in patients with acute renal failure, as it selectively activates renal dopamine DA1 receptor without affecting additional receptors, lowers renal vascular resistance, and increases urinary output [21].

Dosing Options

Oral bioavailability is poor, limiting administration to continuous intravenous infusion. The initial infusion rate is 0.03–0.1 mcg/kg/min and increased in increments of 0.05–0.1 mcg/kg/min every 15 min until targeted response is reached. The maximal infusion rate is 1.6 mcg/kg/min. In children under the age of 12 years, the initial infusion rate is 0.2–0.3 mcg/kg/min and is titrated up to a maximum dose, 0.8 mcg/kg/min. The onset of action is 5 min and the peak effect is reached within 20 min. The medication is rapidly metabolized by the liver and excreted in the urine [6].

Drug Interaction and Contraindications

No drug interaction is reported. There are no contraindications.

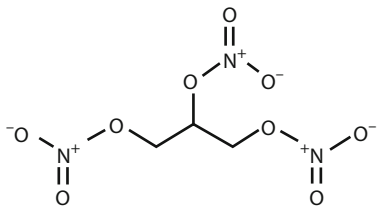
Side Effects

The drug increases intraocular pressure and decreases serum potassium levels. The other side effects are related to vasodilation, which included hypotension, dizziness, headache, flushing, and tachycardia.

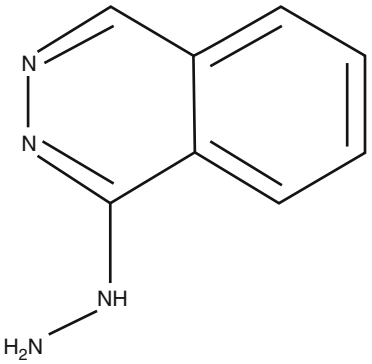
Clinical Pearls

I. Fenoldopam contains sulfite and is therefore contraindicated in patients with a sulfur allergy.
II. Fenoldopam may increase intraocular pressure. Monitor patients for any changes in vision during and after the treatment [21].
III. Monitoring of potassium levels is required to prevent dangerous hypokalemia [21].

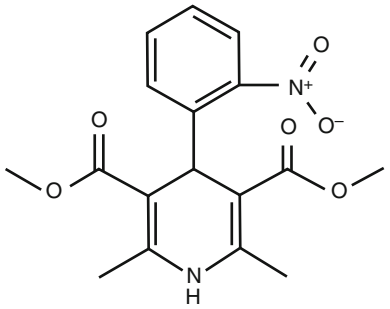
Chemical Structures



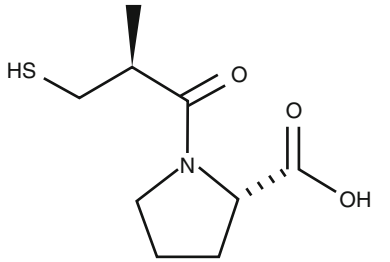
Chemical Structure 16.1 Nitroglycerin



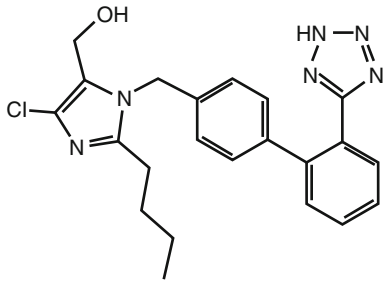
Chemical Structure 16.2 Hydralazine



Chemical Structure 16.3 Nifedipine



Chemical Structure 16.4 Captopril



Chemical Structure 16.5 Losartan

References

1. Studies PSUOotVPfRaG, School PSUOotVPfRaDotG. Research/Penn State: Pennsylvania State University, Office of the Vice President for Research and Graduate Studies. 1998.
2. Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, Smith R, Dunkman WB, Loeb H, Wong M. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med. 1991;325:303–10.
3. Loeb HS, Johnson G, Henrick A, Smith R, Wilson J, Cremo R, Cohn JN. Effect of enalapril, hydralazine plus isosorbide dinitrate, and prazosin on hospitalization in patients with chronic congestive heart failure. The V-HeFT VA Cooperative Studies Group. Circulation. 1993;87:VI78–87.
4. Rector TS, Johnson G, Dunkman WB, Daniels G, Farrell L, Henrick A, Smith B, Cohn JN. Evaluation by patients with heart failure of the effects of enalapril compared with hydralazine plus isosorbide dinitrate on quality of life. V-HeFT II. The V-HeFT VA Cooperative Studies Group. Circulation. 1993;87:VI71–7.
5. Meinertz T. Nitroglycerin 9: nitrates and mobility. Berlin: Walter de Gruyter; 2000.
6. In: Lexi-Drugs Online [Internet Database]. Hudson OL-C, Inc. Accessed 26 Mar 2014.
7. Kannam JP, Gersh BJ. Nitrates in the management of stable angina pectoris. In: Biller J, Wilterdink JL, GM, editors. Uptodate Inc. Retrieved from http://www.uptodatecom/home/indexhtml. Accessed 25 Mar 2014.
8. Irwin RS, Rippe JM. Irwin and Rippe's intensive care medicine. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008.
9. Kaplan NM. Drug treatment of hypertensive emergencies. In: Aronson MD, Holt NF, Sokol HN, editors. Uptodate Inc. Retrieved from http://www.uptodatecom/home/indexhtml. Accessed 25 Mar 2014.
10. Hensley FA, Gravlee GP, Martin DE. A practical approach to cardiac anesthesia. 4th ed. Philadelphia: Wolters Kluwer Health; 2008.
11. Barash PG, Cullen BF, Stoelting RK, Cahalan M, Stock C. Clinical anesthesia. 6th ed. Philadelphia: Wolters Kluwer Health; 2009.
12. Feldman AM. Heart failure: pharmacologic management. Hoboken: Wiley; 2008.
13. Agasti TK. Textbook of anaesthesia for postgraduates. New Delhi: Jaypee Brothers, Medical Publishers; 2011.
14. Izzo JL, Black HR, Goodfriend TL, Research CHBP. Hypertension primer: the essentials of high blood pressure. Philadelphia: Lippincott Williams & Wilkins; 2003.
15. Goljan EF. Rapid review pathology: with student consult online access. Elsevier – Health Sciences Division.
16. Modak RK. Anesthesiology Keywords Review. 2nd ed. Philadelphia: Wolters Kluwer Health; 2013.
17. Singer RJ, Ogilvy CS, Rordof G. Treatment of aneurysmal subarachnoid hemorrhage. In: Kaski JC, Shaperia GM, editors. Uptodate Inc. Retrieved from http://www.uptodatecom/home/indexhtml. Accessed 25 Mar 2014.
18. Schaefer C, Peters PWJ, Miller RK. Drugs during pregnancy and lactation: treatment options and risk assessment. 2nd ed. London: Elsevier Science; 2007.
19. Hines RL, Marschall K. Stoelting's anesthesia and co-existing disease. 5th ed. Philadelphia: Churchill Livingstone; 2008.
20. Lovich-Sapola JA. Anesthesia oral board review: knocking out the boards. New York: Cambridge University Press; 2009.
21. Frishman WH, Sica DA. Cardiovascular pharmacotherapeutics. 3rd ed. Minnesota: Cardiotext Publishing; 2011.