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3B. Gawat darurat
Lulusan dokter mampu membuat diagnosis klinik dan memberikan terapi pendahuluan pada keadaan gawat darurat demi menyelamatkan nyawa atau mencegah keparahan dan/atau kecacatan pada pasien. Lulusan dokter mampu menentukan rujukan yang paling tepat bagi penanganan pasien selanjutnya. Lulusan dokter juga mampu menindaklanjuti sesudah kembali dari rujukan.

Tingkat Kemampuan 4: mendiagnosis, melakukan penatalaksanaan secara mandiri dan tuntas

Lulusan dokter mampu membuat diagnosis klinik dan melakukan penatalaksanaan penyakit tersebut secara mandiri dan tuntas.

4A. Kompetensi yang dicapai pada saat lulus dokter

4B. Profisiensi (kemahiran) yang dicapai setelah selesai internsip dan/atau Pendidikan Kedokteran Berkelanjutan (PKB)

Hipertensi Esensial

No ICPC II : K86 *Hypertension uncomplicated*
No ICD X : I10 *Essential (primary) hypertension*

Tingkat Kemampuan:
4A

Masalah Kesehatan

Hipertensi adalah kondisi terjadinya peningkatan tekanan darah sistolik lebih dari ≥ 140 mmHg dan atau diastolik ≥ 90 mmHg.

Kondisi ini sering tanpa gejala. Peningkatan tekanan darah yang tidak terkontrol dapat mengakibatkan komplikasi, seperti stroke, aneurisma, gagal jantung, serangan jantung dan kerusakan ginjal.

Pemberian obat anti hipertensi merupakan pengobatan jangka panjang. Kontrol pengobatan dilakukan setiap 2 minggu atau 1 bulan untuk mengoptimalkan hasil pengobatan.

a. Hipertensi tanpa *compelling indication*
   1. Hipertensi stage-1 dapat diberikan diuretik (HCT 12.5-50 mg/hari, furosemid 2x20-80 mg/hari), atau pemberian penghambat ACE (captopril 2x25-100 mg/hari atau enalapril 1-2 x 2,5-40 mg/hari), penyekat reseptor beta (atenolol 25-100mg/hari dosis tunggal), penghambat kalsium (diltiazem *extended release* 1x180-420 mg/hari, amlodipin 1x2,5-10 mg/hari, atau nifedipin *long acting* 30-60 mg/hari) atau kombinasi.
   2. Hipertensi stage-2.
   3. Bila target terapi tidak tercapai setelah observasi selama 2 minggu, dapat diberikan kombinasi 2 obat, biasanya golongan diuretik, tiazid dan penghambat ACE atau antagonis reseptor AII (losartan 1-2 x 25-100 mg/hari) atau penyekat reseptor beta atau penghambat kalsium.
   4. Pemilihan anti hipertensi didasarkan ada tidaknya kontraindikasi dari masing-masing antihipertensi diatas.Sebaiknya pilih obat hipertensi yang diminum sekali sehari atau maksimum 2 kali sehari.

b. Hipertensi *compelling indication* (lihat tabel)
   Bila target tidak tercapai maka dilakukan optimalisasi dosis atau ditambahkan obat lain sampai target tekanan darah tercapai (kondisi untuk merujuk ke Spesialis).

Tabel 25. Hipertensi compelling indication

Indikasi khusus	Obat yang direkomendasikan					
	Diuretik	Penyekat beta (BB)	Penghambat ACE (ACEi)	Antagonis reseptor AII (ARB)	Penghambat kanal kalsium (CCB)	Antagonis aldosteron
Gagal jantung	√	√	√	√		√
Pasca infark miokard akut		√	√			√
Risiko tinggi penyakit koroner	√	√	√		√	
DM	√	√	√	√	√	
Penyakit ginjal kronik			√	√		
Pencegahan stroke berulang	√		√			

c. Kondisi khusus lain
   1. *Obesitas dan sindrom metabolik*
      Lingkar pinggang laki-laki >90 cm/perempuan >80 cm. Tolerasi glukosa terganggu dengan GDP ≥ 110 mg/dl, tekanan darah minimal 130/85 mmHg, trigliserida tinggi ≥150 mg/dl, kolesterol HDL rendah <40 mg/dl (laki-laki) dan <50 mg/dl (perempuan) Modifikasi gaya hidup yang intensif dengan terapi utama ACE, pilihan lain reseptor AII, penghambat calsium dan penghambat Ω.
   2. *Hipertrofi ventrikel kiri*

Tatalaksana tekanan darah agresif termasuk penurunan berat badan, restriksi asupan natrium dan terapi dengan semua kelas antihipertensi kecuali vasodilator langsung, yaitu hidralazin dan minoksidil.

3. *Penyakit Arteri Perifer*
   Semua kelas antihipertensi, tatalaksana faktor risiko dan pemberian aspirin.
4. *Lanjut Usia*
   Diuretik (tiazid) mulai dosis rendah 12,5 mh/hari.
   Obat hipertensi lain mempertimbangkan penyakit penyerta.
5. *Kehamilan*
   Golongan metildopa, penyekat reseptor β, antagonis kalsium, vasodilator.
   Penghambat ACE dan antagonis reseptor AII tidak boleh digunakan selama kehamilan.

Target dan Tujuan

Target terapi pada usia > 60 tahun dengan tekanan darah sistolik > 150 mmHg dan diastolik > 90 mmHG. Tujuan terapi adalah tekanan darah < 150/90 mmHg

Target terapi pada usia < 60 tahun dengan tekanan darah sistolik > 140 mmHg dan diastolik > 90 mmHG. Tujuan terapi adalah tekanan darah < 140/90 mmHg

Target terapi pada penderita disertai diabetes melitus dengan tekanan darah sistolik > 140 mmHg dan diastolik > 90 mmHG. Tujuan terapi adalah tekanan darah < 140/90 mmHg

Target terapi pada penderita disertai gangguan ginjal kronik dengan tekanan darah sistolik > 140 mmHg dan diastolik > 90 mmHG. Tujuan terapi adalah tekanan darah < 140/90 mmHg

Rekomendasi pemberian obat awal (JNC 8)

Guideline	Population	Goal BP, mm Hg	Initial Drug Treatment Options
2014 Hypertension guideline	General ≥60 y	<150/90	Nonblack: thiazide-type diuretic, ACEI, ARB, or CCB; black: thiazide-type diuretic or CCB
	General <60 y	<140/90	
	Diabetes	<140/90	Thiazide-type diuretic, ACEI, ARB, or CCB
	CKD	<140/90	ACEI or ARB

Obat yang tersedia di layanan primer (Formularium Nasional BPJS 2014)

amlodipin*		
1.	tab 5 mg	√
2.	tab 10 mg	√
atenolol*		
1.	tab 50 mg	√
2.	tab 100 mg	
hidroklorotiazid*		
1.	tab 25 mg	√
kaptopril*		
1.	tab 12,5 mg	√
2.	tab 25 mg	
3.	tab 50 mg	
klortalidon*		
1.	tab 50 mg	√
nifedipin*		
1.	kaps 10 mg	√
	Hanya untuk preeklampsia dan tokolitik.	
2.	tab SR 20 mg	
3.	tab SR 30 mg	
propranolol*		
1.	tab 10 mg	√

Amlodipine

Norvasc

Drug Information Provided By Gold Standard

Description:

Amlodipine is an oral calcium-channel blocker. It is used for the treatment of hypertension, chronic stable angina pectoris, and Prinzmetal's variant angina. Amlodipine is considered less effective than ACE inhibitors or AII-receptor antagonists in slowing the progression of renal disease in patients with diabetic nephropathy or hypertensive renal disease.

26714 26715

Amlodipine is a potent peripheral vasodilator, similar to nifedipine and other members of the dihydropyridine class, although amlodipine has the longest half-life of the group, thus allowing for once-daily dosing. Amlodipine besylate (Norvasc®) was approved by the FDA in July 1992. The FDA has withdrawn the 2003 approval for amlodipine maleate (AmVaz®); this drug was a different salt form of amlodipine (not generically equivalent to amlodipine besylate) and was initially approved on November 2, 2003. The US Federal Court has ruled that AmVaz® infringes on patent rights held by Pfizer for Norvasc® (March, 2004). Sepracor has conducted Phase I and II studies with the S-isomer of amlodipine for the treatment of hypertension. In theory, less potential for peripheral edema may exist with S-amlodipine. The FDA has approved amlodipine for use in patients with recently documented coronary artery disease (CAD) by angiography and without heart failure (September 2005). The CAMELOT trial has demonstrated that amlodipine use in patients with documented CAD results in reduced coronary revascularization procedures and reduced hospitalizations due to angina.

29090 31509

Mechanism of Action:

Amlodipine inhibits the influx of extracellular calcium across the myocardial and vascular smooth muscle cell membranes. Serum calcium levels remain unchanged. Amlodipine inhibits this influx, and the resultant decrease in intracellular calcium inhibits the contractile processes of the myocardial smooth muscle cells, resulting in dilation of the coronary and systemic arteries. As with other calcium-channel blockers of the dihydropyridine class, amlodipine exerts its effects mainly on arteriolar vasculature. It has no significant effect on sinus node function or cardiac conduction, nor does it possess negative inotropic effects at clinical doses. Because it has a gradual onset, reflex tachycardia does not occur, a side effect that is common with other peripheral vasodilators. Amlodipine therapy usually does not affect hemodynamic parameters in patients with normal ventricular function.

Amlodipine reduces coronary vascular resistance and increases coronary blood flow. These actions increase oxygen delivery to the myocardial tissue. Myocardial oxygen consumption is also reduced. Thus, amlodipine's beneficial effects in the treatment of angina are a result of multiple actions. In general, calcium-channel blockers exert favorable effects on LVH, and do not worsen insulin resistance or exert detrimental effects on the lipid profile.

Pharmacokinetics:

Amlodipine is administered orally. Like other calcium-channel blockers, it is primarily metabolized by CYP3A4 isoenzymes. The drug is approximately 93% bound to plasma proteins, but drug interactions secondary to displacement from binding sites have not been documented. Amlodipine is extensively metabolized to inactive compounds, and 10% of the parent compound and 60% of the inactive metabolites are excreted in the urine. The terminal half-life is about 30—50 hours, which is significantly longer than other dihydropyridines that are currently available.

For the treatment of hypertension:

NOTE: The maximum hypotensive effects may require several weeks to become fully manifest.
Oral dosage:
Adults: Initially, 5 mg PO once daily. Maximum dosage is 10 mg once daily. Dosage should be adjusted based on clinical response over a period of 7—14 days. The usual dosage is 5—10 mg PO once daily.
Geriatric and Debilitated patients: Reduce initial dosage to 2.5 mg PO once daily, then may increase to 5 mg PO once daily. Maximum 10 mg/day, based on tolerance and clinical response.
Adolescents and Children >= 6 years: 2.5—5 mg PO once daily based on a randomized, double-blind, placebo-controlled study of 268 hypertensive pediatric patients ages 6—16 years.

Atenolol

Tenormin

Drug Information Provided By Gold Standard

Description:

Atenolol is a competitive, beta-1-selective adrenergic antagonist, similar to metoprolol. Atenolol has a longer plasma half-life than does metoprolol, which allows for once-daily dosing. Due to its low-lipid solubility, atenolol is renally eliminated, minimally metabolized, and has a lower potential for inducing CNS side effects compared to lipid-soluble beta-blockers (e.g., propranolol). As with other 'cardioselective' beta-blockers, high doses result in attenuated or lost selectivity for the beta-1-receptor. Unlike pindolol, atenolol does not have intrinsic sympathomimetic properties. Atenolol also does not possess membrane-stabilizing activity as pindolol and propranolol do. The 2007 AHA guidelines for the management of hypertension state beta-blockers should not be used as first-line therapy for the treatment of hypertension, as several comparative clinical trials have shown beta blockers to be inferior to ACE inhibitors, angiotensin-receptor blockers, or calcium channel blockers for preventing both stroke and

coronary artery disease complications. These guidelines do, however, recommend the use of beta-blockers for the treatment of hypertension in patients with angina, prior myocardial infarction, or heart failure.

33826

Atenolol was approved by the FDA in 1981.

Mechanism of Action:

Beta-adrenergic antagonists counter the effect of sympathomimetic neurotransmitters (i.e., catecholamines) by competing for receptor sites. Similar to metoprolol, atenolol, in low doses, selectively blocks sympathetic stimulation mediated by $beta_1$-adrenergic receptors in the heart and vascular smooth muscle. The pharmacodynamic consequences of this activity include: reduction of resting heart rate and, subsequently, cardiac output; reduction of both systolic and diastolic blood pressure at rest and with exercise; and possible reduction of reflex orthostatic hypotension. With higher doses (>100 mg/day), atenolol also competitively blocks $beta_2$-adrenergic responses in the bronchial and vascular smooth muscles. In addition, serum free fatty acid concentrations are decreased and triglyceride levels increased by atenolol.

A critical effect of beta blockade is to provide prophylaxis and reduction in myocardial ischemia and potentially prevent the severity of subsequent myocardial infarction. Part of this effect also may be attributed to the antiarrhythmic properties of beta blockade at the nodal level of pacemaker control.

Actions that make atenolol useful in treating hypertension include: a negative chronotropic effect that decreases heart rate at rest and after exercise; a negative inotropic effect that decreases cardiac output; reduction of sympathetic outflow from the CNS; and suppression of renin release from the kidneys. Thus, atenolol, like other beta-blockers, affects blood pressure via multiple mechanisms. In general, beta-blockers without intrinsic sympathomimetic activity (ISA) exert detrimental effects on LVH and the lipid profile, and cause sexual dysfunction.

Atenolol is used to treat angina because the drug decreases the oxygen demand of the heart, both by decreasing heart rate and contractility and by lowering blood pressure. However, in patients with cardiac failure, the opposite may be true (i.e., the drug can increase the oxygen demand of the heart.)

Atenolol possesses numerous mechanisms that may contribute to its efficacy in preventing migraine headaches.

23792

Beta-blockade can prevent arterial dilation, inhibit renin secretion, and block catecholamine-induced lipolysis. Blocking lipolysis, decreases arachidonic acid synthesis and subsequent prostaglandin production. Inhibition of platelet aggregation is due to this decrease in prostaglandins and blockade of catecholamine-induced platelet adhesion. Other actions include increased oxygen delivery to tissues and prevention of coagulation during epinephrine release.

Pharmacokinetics:

Atenolol is administered orally and parenterally. Effects on blood pressure do not coincide with effects on heart rate, nor does the antihypertensive effect exhibit a linear dose/pharmacodynamic response. Atenolol is distributed throughout the body and into breast milk. It also crosses the placenta, with fetal serum atenolol concentrations approaching those of the mother. Unlike propranolol, atenolol distribution into the CNS by crossing the blood-brain barrier is minimal. Atenolol is minimally bound to plasma proteins, averaging only 10%, which, along with it low lipophilicity, may explain some of its distribution characteristics. Atenolol undergoes little or no metabolism by the liver, and the absorbed portion is eliminated primarily by renal excretion. Over 85% of an intravenous dose is excreted in urine within 24 hours compared with approximately 50% for an oral dose. The rest of the dose is excreted via the fecal route as unchanged drug. The serum half-life of atenolol in patients with normal renal function is 6—7 hours in adults.

For the treatment of hypertension:

NOTE: The 2007 AHA guidelines for the management of hypertension recommend beta-blockers should only be used as first-line therapy for the treatment of hypertension in patients with angina, prior myocardial infarction, or heart failure.

Oral dosage:

Adults: Initially, 25—50 mg PO once daily. Increase up to 100 mg/day if needed after 7—14 days. Further increases generally will have no increased therapeutic effect, although daily doses of up to 200 mg have been efficacious.

Elderly: Initiate therapy at the lower end of the adult dosage range (e.g., 25—50 mg PO

once daily). Titrate dosage to attain therapeutic goals, including an assessment of trough blood pressure to ensure 24 hour effectiveness. Maximum dose: 100 mg/day.
Children: Initially, 0.8—1 mg/kg PO once daily. The usual dosage range is 0.8—1.5 mg/kg/day. Maximum dose is 2 mg/kg/day.

Hydrochlorothiazide, HCTZ

Esidrix | Ezide | HCT 50 | HydroDIURIL | HydroKraft ...

Drug Information Provided By Gold Standard

Description:

Hydrochlorothiazide (HCTZ) is a thiazide diuretic used in the management of edema and hypertension. In hypertension, thiazide diuretics are often used as initial therapy, either alone or in combination with other agents. Unlike the loop diuretics, their efficacy is diminished in patients with renal insufficiency. Hydrochlorothiazide also has been used to treat diabetes insipidus and hypercalciuria, although these are not FDA-approved indications. Hydrochlorothiazide was approved by the FDA in 1959.

Mechanism of Action:

Thiazide diuretics increase the excretion of sodium, chloride, and water by inhibiting sodium ion transport across the renal tubular epithelium. Although thiazides may have more than one action, the major mechanism responsible for diuresis is to inhibit active chloride reabsorption at the distal portion of the ascending limb or, more likely, the early part of the distal tubule (i.e., the cortical diluting segment). Exactly how chloride transport is impaired is unknown. Thiazides also increase the excretion of potassium and bicarbonate, and they decrease the urinary excretion of calcium and uric acid. Hydrochlorothiazide may be used to reduce hypercalciuria and prevent the recurrence of calcium-containing renal calculi. By increasing the sodium load at the distal renal tubule, hydrochlorothiazide indirectly increases potassium excretion via the sodium-potassium exchange mechanism. Hypochloremia and hypokalemia can cause mild metabolic alkalosis. The diuretic efficacy of hydrochlorothiazide is not affected by the acid-base balance of the patient. Hydrochlorothiazide is not an aldosterone antagonist, and its main action is independent of carbonic anhydrase inhibition.

The antihypertensive mechanism of hydrochlorothiazide is unknown. It usually does not affect normal blood pressure. Initially, diuretics lower blood pressure by decreasing cardiac output and reducing plasma and extracellular fluid volume. Cardiac output eventually returns to

normal, plasma and extracellular fluid values return to slightly less than normal, but peripheral vascular resistance is reduced, resulting in lower blood pressure. These diuretics also decrease the glomerular filtration rate, which contributes to the drug's lower efficacy in patients with renal impairment. The changes in plasma volume induce an elevation in plasma renin activity, and aldosterone secretion is increased, contributing to the potassium loss associated with thiazide diuretic therapy. In general, diuretics worsen glucose tolerance and exert detrimental effects on the lipid profile.

Pharmacokinetics:

Hydrochlorothiazide is administered orally. The drug crosses the placenta, but not the blood-brain barrier, and is distributed into breast milk. Hydrochlorothiazide is not significantly metabolized and is excreted unchanged in the urine. At least 61% of the oral dose is eliminated unchanged within 24 hours. The elimination half-life ranges from 5.6—14.8 hours.

For the treatment of hypertension:

Oral dosage:

Adults and Adolescents: Initially, 12.5—25 mg PO once daily. Dosage may be increased, if necessary, up to 50 mg/day PO given in 1—2 divided doses. Although the manufacturer's recommended maintenance dosage is 25—100 mg PO per day, expert panels on the treatment of hypertension recommend the addition of another antihypertensive agent if blood pressure is not controlled with 25—50 mg/day of hydrochlorothiazide.

24233

In a double-blind randomized study, the effects of 25 mg/day vs. 50 mg/day of hydrochlorothiazide were evaluated in geriatric patients (n = 51) with isolated systolic hypertension. Both dosages were associated with similar reductions in blood pressure; however, the higher dose (50 mg/day) caused a greater decline in serum potassium concentration.

25037

Geriatric: See adult dosage. Geriatric patients may be more sensitive to the effects of the usual adult dosage.

Infants >= 6 months and Children: 1—2 mg/kg/day PO, given in a single dose or 2 divided doses, not to exceed 37.5 mg/day for infants >= 6 months and children up to 2 years or 100 mg/day in children 2—12 years.

41355

Neonates and Infants < 6 months: 2—3.3 mg/kg/day PO given in 2 divided doses has been recommended by some pediatric experts

41517

; however, 3 mg/kg/day PO is the highest dosage recommended by the manufacturer.

41355

Captopril

Capoten

Drug Information Provided By Gold Standard

Description:

Captopril is an angiotensin-converting enzyme (ACE) inhibitor used in the treatment of hypertension, congestive heart failure, and various renal syndromes such as diabetic nephropathy and scleroderma. Captopril is the first ACE inhibitor to have been marketed in the United States. Captopril has been shown to significantly reduce mortality in patients with heart failure. As the shortest-acting of all ACE inhibitors, it is usually dosed two or three times a day. Captopril contains a sulfhydryl group, which may contribute to its pharmacologic action and account for some adverse reactions that occur at higher doses. Captopril was approved by the FDA in 1981. Its patent expired on February 13, 1996.

Mechanism of Action:

Captopril has a high affinity for ACE and competes with angiotensin I, the natural substrate, to block its conversion to angiotensin II. Angiotensin II is a potent vasoconstrictor and a negative feedback mediator for renin activity. Thus, as a result of lower angiotensin II plasma levels, blood pressure decreases and plasma renin activity increases. In addition, baroreceptor reflex mechanisms are stimulated by the drop in blood pressure. Kininase II, identical to ACE, is an enzyme that degrades bradykinin, a potent vasodilator, to inactive peptides. Whether increased bradykinin levels play a part in the therapeutic effects of ACE inhibitors is presently unclear. Bradykinin-induced vasodilation is thought to be of secondary importance in the blood-pressure

lowering effect of ACE inhibitors. A bradykinin mechanism may, however, contribute to ACE-inhibitor-induced angioneurotic edema and cough.

24005

The "local" activity of ACE inhibitors may be more responsible for their clinical effects than systemic activity. ACE-inhibiting drugs may act locally (i.e., within a specific tissue) to reduce vascular tone by decreasing local angiotensin II-induced sympathetic activity and/or by decreasing local angiotensin II-induced vasoconstrictive activity. ACE inhibitors may inhibit presynaptic norepinephrine release and postsynaptic adrenergic receptor activity, decreasing vascular sensitivity to vasopressor activity. Decreases in plasma angiotensin II levels reduce aldosterone secretion, with a subsequent decrease in sodium and water retention.

Captopril dilates arterioles, thereby lowering total peripheral vascular resistance. In hypertensive patients, blood pressure is decreased with little or no change in heart rate, stroke volume, or cardiac output. However, captopril can increase cardiac output, cardiac index, stroke volume, and exercise tolerance in patients with congestive heart failure. The drug also decreases pulmonary wedge pressure, pulmonary vascular resistance, and mean arterial and right atrial pressures in these patients. As antihypertensives, ACE inhibitors reduce LVH, do not worsen insulin resistance or hyperlipidemia, and do not cause sexual dysfunction.

Pharmacokinetics:

Captopril is administered orally. Captopril distributes into most body tissues, and approximately 25% is bound to proteins. The drug is metabolized (50%) in the liver to inactive metabolites, followed by excretion of the unchanged drug and its metabolites in the urine. Captopril renal elimination occurs primarily by tubular excretion. In patients with normal renal function, the half-life of captopril is less than 2 hours.

For the treatment of hypertension:

Oral dosage:

Adults: Initially, 12.5—25 mg PO, given 2—3 times per day. May increase to 50 mg PO three times daily after 1—2 weeks if needed. A diuretic may be added after 1—2 weeks if needed. If patient is already receiving a diuretic, lower initial doses should be used. Maintenance dosage

range is 25—150 mg PO 2—3 times per day. The maximum daily dose is 150 mg three times per day; this daily dose of 450 mg may also be given in 2 divided doses per day. Most clinicians recognize 150 mg/day as the effective maximum daily dose, above which adverse reactions increase.
Geriatric: Initiate therapy at the lower end of the adult dosage range. Greater sensitivity to the usual adult dose is possible. Adjust dosage based on clinical response.
Children† and Adolescents†: Initially, 0.3—0.5 mg/kg PO per dose. Maximum dosage is 6 mg/kg/day, given in 2—4 divided doses.

42868

Although a specific total mg maximum dose has not been clearly defined, initial and final doses should not exceed those recommended for adult patients (e.g. 12.5—25 mg/dose for initial doses and 450 mg/day for the final dose).
Infants†: Initially, 0.15—0.3 mg/kg PO per dose. Maximum dosage is 6 mg/kg/day, given in 1—4 divided doses. The usual dosage is 2.5—6 mg/kg/day.
Neonates†: Initially, 0.01—0.1 mg/kg/dose PO every 8—24 hours. Titrate dose up based on clinical response to 0.5 mg/kg/dose PO every 6—24 hours.

Chlorthalidone

Thalitone

Drug Information Provided By Gold Standard

Description:

Chlorthalidone is a thiazide-like diuretic used in the management of hypertension and edema. Its structure and pharmacological activity are similar to the thiazides. Compared to other thiazides, chlorthalidone has the longest duration of action, but the diuretic effect is basically equal among the thiazides at maximal therapeutic doses. Unlike loop diuretics, chlorthalidone efficacy is diminished in patients with renal insufficiency. A recent landmark clinical trial (ALLHAT) compared chlorthalidone to doxazosin in the treatment of high-risk hypertensive patients. In this study, only chlorthalidone significantly reduced the risk of combined cardiovascular disease events, especially heart failure; whereas doxazosin did not.

26195

These results led to discontinuation of the doxazosin treatment arm of the study. Chlorthalidone was approved by the FDA in 1960.

Mechanism of Action:

Chlorthalidone increases the excretion of sodium, chloride, and water by inhibiting sodium ion transport across the renal tubular epithelium. Its primary site of action is in the cortical diluting segment of the ascending limb of the loop of Henle. Thiazides and related compounds also decrease the glomerular filtration rate, which further reduces the drug's efficacy in patients with renal impairment. By increasing the delivery of sodium to the distal renal tubule, chlorthalidone indirectly increases potassium excretion via the sodium-potassium exchange mechanism. Hypokalemia and hypochloremia may cause mild metabolic alkalosis. However, the diuretic efficacy of chlorthalidone is not affected by the acid-base balance in the patient. Chlorthalidone is not an aldosterone antagonist, and its actions are independent of carbonic anhydrase inhibition.

Initially, diuretics lower blood pressure by decreasing cardiac output and reducing plasma and extracellular fluid volume. Eventually, cardiac output returns to normal, and plasma and extracellular fluid volume return to slightly less than normal, but a reduction in peripheral vascular resistance is maintained, resulting in lower blood pressure. The reduction in plasma volume induces an elevation in plasma renin activity and aldosterone secretion, further contributing to the potassium loss associated with thiazide diuretic therapy. In general, diuretics worsen glucose tolerance and exert detrimental effects on the lipid profile.

Pharmacokinetics:

Chlorthalidone is administered orally. The drug is 75% bound to plasma proteins and is also highly bound to red blood cells (blood to plasma ratio 72.5), with carbonic anhydrase as the binding site. Chlorthalidone crosses the placenta and is distributed into human breast milk. The onset of action is about 2 hours, with peak effects occurring in 2—6 hours and the duration of action lasting 48—72 hours. The majority of the drug is excreted unchanged in the urine (50—74%), with some potential biliary excretion. The mean half-life of chlorthalidone is approximately 40 to 60 hours.

For the treatment of hypertension:

NOTE: A landmark clinical trial (ALLHAT) compared chlorthalidone to doxazosin in the treatment of high-risk hypertensive patients. In this study, chlorthalidone significantly reduced the risk of combined cardiovascular disease events, especially heart failure. These results led to

discontinuation of the doxazosin treatment arm of the study.

Oral dosage (Hygroton):

Adults: Initially, 25 mg PO daily. Increase if needed to 50 mg PO daily. Dosage above 25 mg generally increases potassium excretion without additional blood pressure reduction.

Elderly: See adult dosage. Elderly patients may be more sensitive to the effects of the usual adult dosage.

Children: Suggested dose is 2 mg/kg/day or 60 mg/m^2/day PO three times weekly, adjusted based on patient response.

Oral dosage (Thalitone):

Adults: Initiate therapy at 15 mg PO once daily as a single dose. Increase if needed to 30 mg PO once daily, and then to 45—50 mg PO once daily. If additional control is required, the manufacturer recommends addition of a second antihypertensive agent. Increases in serum uric acid and decreases in serum potassium are dose-related over the 15—50 mg/day range and beyond.

Elderly: See adult dosage. Elderly patients may be more sensitive to the effects of the usual adult dosage.

Children, Infants, or Neonates: Safety and efficacy have not been established.

Nifedipine

Adalat | Adalat CC | AfeditabCR | Nifediac CC | Nifedical XL ...

Drug Information Provided By Gold Standard

Description:

Nifedipine is the prototype of the dihydropyridine class of calcium-channel antagonists. It is structurally and pharmacologically similar to other dihydropyridines including amlodipine, felodipine, isradipine, and nicardipine. In general, the dihydropyridine-type calcium-channel antagonists have more prominent effects on vasodilation and coronary flow relative to diltiazem and verapamil. Unlike both diltiazem and verapamil, however, nifedipine has negligible effects on AV nodal conduction. This difference is attributed to the fact that nifedipine binds to a different site in the calcium channel. Nifedipine is used in the treatment of Prinzmetal's angina, hypertension, and other vascular disorders such as Raynaud's phenomenon†. Nifedipine is available in immediate-release and extended-release dosage forms. The immediate-release nifedipine dosage forms should only be used to treat patients with chronic stable or vasospastic

angina angina; the immediate-release formulation is associated with serious side effects when used to treat patients with hypertension, hypertensive urgency, hypertensive emergency, or coexisting myocardial infarction.

24732

Although its actions were described in 1972, nifedipine was not approved by the FDA until 1981.

Mechanism of Action:

Like other calcium-channel antagonists, nifedipine inhibits the influx of extracellular calcium through myocardial and vascular membrane pores, which are selective for specific ions. Serum calcium levels remain unchanged. It is believed that nifedipine inhibits this influx by physically plugging the channel. While verapamil and diltiazem exert balanced effects on calcium channels in the SA node, AV node, and vasculature, nifedipine and other members of the dihydropyridine group act predominantly on the vasculature, making these agents more potent peripheral vasodilators. The decrease in intracellular calcium inhibits the contractile processes of smooth muscle cells, causing dilation of the coronary and systemic arteries. This results in increased oxygen delivery to the myocardial tissue, decreased total peripheral resistance, decreased systemic blood pressure, and decreased afterload.

Although these drugs originally were believed to improve oxygen supply, it now appears that their effectiveness as anti-ischemic agents arises from their ability to alter the systemic balance between supply and demand. Reduced afterload and reduced myocardial wall tension lead to reduced myocardial oxygen demand, which now seems to best explain the benefit of nifedipine and other dihydropyridines in the treatment of angina. Thus, nifedipine increases myocardial oxygen supply (secondary to coronary vasodilation) and decreases myocardial oxygen demand (secondary to decreased afterload). Nifedipine appears particularly effective in treating variant angina (i.e., vasospastic angina) due to this ability to increase myocardial oxygen supply by inducing coronary vasodilation. The effectiveness of nifedipine in treating chronic stable angina, on the other hand, is related to the decrease in myocardial oxygen demand secondary to decreased afterload.

Nifedipine has no clinical effect on AV conduction, which may be due to its inhibition of phosphodiesterase. This intracellular mechanism of nifedipine actually enhances calcium inflow and counteracts its own inhibitory effects on calcium influx at the membrane surface. Also, phosphodiesterase inhibition causes additional relaxation of vascular smooth muscle. Thus,

nifedipine is more potent than verapamil as a peripheral vasodilator but has negligible effects on AV nodal conduction. Negative inotropic effects rarely are noted clinically, presumably due to a reflex increase in heart rate in response to nifedipine's vasodilatory activity. Nifedipine therapy usually does not affect cardiovascular parameters in patients with normal ventricular function, but patients with decreased left ventricular function can experience an increase in ejection fraction and a decrease in left ventricular filling pressures. In general, calcium-channel blockers exert favorable effects on LVH, and do not worsen insulin resistance or exert detrimental effects on the lipid profile.

Pharmacokinetics:

Nifedipine is administered orally and sublingually. It is relatively well distributed, including into breast milk. Nifedipine is protein-bound in a concentration-dependent way, ranging from 92—98%. Hepatic metabolism is rapid and complete, causing the formation of two inactive metabolites that, along with the parent drug, are excreted primarily in the urine and, to a lesser extent, the feces. Less than 5% is eliminated as unchanged drug. The elimination half-life is approximately 2—5 hours.

Affected cytochrome P450 isoenzymes and drug transporters: CYP3A4, P-gp
Nifedipine is a CYP3A4 substrate, and its metabolism may be affected by CYP3A4 inhibitors or inducers.

31749

Nifedipine also is a mild inhibitor of P-glycoprotein (P-gp).

For the treatment of hypertension:

Oral dosage - extended-release tablets:
Adults: Initially, 30—60 mg PO once daily. Titrate upwards as necessary. Maximum dosage recommended by the product labeling is 90 mg/day for most formulations of extended-release products; however, the maximum dosing for Procardia XL is 120 mg/day.
Geriatric: See adult dosage. In general, initiate dosage at the lower end of the adult dosage range. Nifedipine plasma concentrations and half-life are significantly increased in geriatric patients. Adjust dosage based on clinical response.
Children† and Adolescents†: Initial doses ranging from 0.25 to 0.5 mg/kg/day PO have

been suggested. Titration as needed up to a maximum of 3 mg/kg/day PO, not to exceed 120 mg/day, has been recommended by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents
31366
; however, some experts recommend that doses up to 180 mg/day may be necessary in some clinical situations.
32338
Dosage may be given once daily or in 2 divided doses administered every 12 hours.
32337 32338
NOTE: Extended-release tablets must be swallowed whole and are too large for young children.

Propranolol

HEMANGEOL | Inderal | Inderal LA | Inderal XL | Innopran XL ...

Drug Information Provided By Gold Standard

Description:

Propranolol is the prototype of the beta-adrenergic receptor antagonists. It is a competitive, nonselective beta-blocker without intrinsic sympathomimetic activity, similar to nadolol. Although propranolol has membrane-stabilizing effects on the action potential, these effects are clinically insignificant except in overdose situations. Propranolol is a racemic compound, with only its l-isomer having any adrenergic blocking activity. The 2007 AHA guidelines for the management of hypertension state beta-blockers should not be used as first-line therapy for the treatment of hypertension, as several comparative clinical trials have shown beta blockers to be inferior to ACE inhibitors, angiotensin-receptor blockers, or calcium channel blockers for preventing both stroke and coronary artery disease complications. These guidelines do, however, recommend the use of beta-blockers for the treatment of hypertension in patients with angina, prior myocardial infarction, or heart failure.

33826

Propranolol was first approved by the FDA in 1967; an extended-release formulation designed for bedtime-dosing was approved in March 2003. Hemangeol, an oral solution specifically

approved for treatment of proliferating infantile hemangiomas, was approved by the FDA in March 2014.

Mechanism of Action:

Like other beta-adrenergic antagonists, propranolol competes with adrenergic neurotransmitters (e.g., catecholamines) for binding at sympathetic receptor sites. Similar to atenolol and metoprolol, propranolol blocks sympathetic stimulation mediated by $beta_1$-adrenergic receptors in the heart and vascular smooth muscle. Pharmacodynamic consequences of $beta_1$-receptor blockade include a decrease in both resting and exercise heart rate and cardiac output, and a decrease in both systolic and diastolic blood pressure. Propranolol may reduce reflex orthostatic hypotension. The fall in cardiac output induced by $beta_1$ effects is often countered by a moderate reflex increase in peripheral vascular resistance that can be magnified by $beta_2$ blockade (unmasked alpha stimulation). As a result, nonselective beta-blocking agents can produce a more modest decrease in (diastolic) blood pressure compared with selective $beta_1$-antagonists. In addition, propranolol also can competitively block $beta_2$-adrenergic responses in the bronchial muscles, potentially inducing bronchospasm.

Actions that make propranolol useful in treating hypertension include a negative chronotropic effect that decreases heart rate at rest and after exercise; a negative inotropic effect that decreases cardiac output; reduction of sympathetic outflow from the CNS; and suppression of renin release from the kidneys. Thus, propranolol, like other beta-blockers, affects blood pressure via multiple mechanisms. In general, beta-blockers without intrinsic sympathomimetic activity (ISA) exert detrimental effects on LVH and the lipid profile, and cause sexual dysfunction.

Actions that make propranolol useful in treating hypertension also apply to managing chronic stable angina. The reduction in myocardial oxygen demand induced by propranolol results in decreases in the frequency of anginal attacks and requirements of nitrate, and increases exercise tolerance. Other postulated anti-anginal actions include an increase in oxygen delivery to tissues, due to propranolol-induced lowering of hemoglobin's affinity for oxygen, and a reduction of platelet aggregation, postulated to be related to interference with calcium ion flux.

Propranolol has been used to treat portal hypertension and to prevent bleeding of esophageal varices. Nonselective beta-blockers decrease portal venous pressure, decrease blood flow in the superior portosystemic collateral circulation, and decrease blood flow in the splanchnic region.

24084

Beta-blockade decreases cardiac output reducing hepatic arterial and portal venous perfusion. Activation of unopposed alpha-receptors lead to splanchnic vasoconstriction, thus decreasing portal perfusion.

Propranolol is used to treat hypertension and the subsequent decline of renal function in patients with scleroderma renal crisis (SRC). SRC is associated with elevated peripheral renin concentrations. Propranolol blocks beta-receptors located on the surface of the juxtaglomerular cells which decreases the release of renin. In turn, this affects the renin-angiotensin-aldosterone system reducing blood pressure.

Numerous mechanisms may contribute to the efficacy of propranolol in preventing migraine headaches.

23792

Beta-blockade can prevent arterial dilation, inhibit renin secretion, and can interfere with catecholamine-induced lipolysis. A decrease in lipolysis decreases arachidonic acid synthesis and, subsequent, prostaglandin production. Inhibition of platelet aggregation is due to this decrease in prostaglandins and blockade of catecholamine-induced platelet adhesion. Other actions include increased oxygen delivery to tissues and prevention of coagulation during epinephrine release.

Propranolol has two roles in the treatment of thyrotoxicosis; these actions are determined by the different isomers of propranolol. L-propranolol causes beta-blockade and can ameliorate the symptoms associated with thytotoxicosis such as tremor, palpitations, anxiety, and heat intolerance. D-propranolol blocks the conversion of T_4 to T_3, but the therapeutic effect of this action is minimal.

24123

Propranolol has been used in the management of hereditary or familial essential tremor. Beta-blockade controls the involuntary, rhythmic and oscillatory movements of essential tremor. Tremor amplitude is reduced, but not the frequency of tremor. The mechanism of action is unclear, but the antitremor effect may be mediated by blockade of peripheral $beta_2$ receptor

mechanisms.

Propranolol can dampen the peripheral physiologic symptoms of anxiety. Beta-blockade can attenuate somatic symptoms of anxiety such as palpitations and tremor, but it is less effective in controlling psychologic components, such as intense fear. These effects are thought to be due to improvement in somatic symptoms secondary to beta-blockade, although the mechanism of action is unclear.

Pharmacokinetics:

Propranolol is administered orally or intravenously. Propranolol is highly lipophilic and is widely distributed throughout the body. It readily crosses the blood-brain barrier and the placenta, and is distributed into breast milk. Propranolol is about 90% bound to plasma proteins, the R(+)-enantiomer primarily binds albumin while the S(-)-enantiomer is primarily bound to alpha-1 acid glycoprotein. The volume of distribution is about 4 L/kg. In normal subjects receiving oral doses of racemic propranolol, S(-)-enantiomer concentrations exceeded those of the R(+)-enantiomer by 40-90% as a result of stereoselective hepatic metabolism.

53617

Propranolol is extensively metabolized upon first pass through the liver, and the extent of metabolism is dependent on liver blood flow. The drug also binds to and saturates nonspecific hepatic binding sites before the drug reaches the systemic circulation. An equipotent, pharmacologically active metabolite, 4-hydroxypropranolol, is produced with the initiation of oral therapy, but it is eliminated faster than the parent drug. With chronic or IV therapy, this metabolite is produced to a lesser degree. Overall, at least eight metabolites of propranolol have been identified. Important differences may exist among ethnic groups in the ability to metabolize propranolol, which can affect the overall efficacy of the drug in some instances. Excretion of propranolol occurs renally, primarily as metabolites, with only 1—4% of a dose excreted fecally as unchanged drug. Clearance of the pharmacologically active S(-)-propranolol is lower than R(+)-propranolol after intravenous and oral doses. The elimination half-life of propranolol ranges from 2—6 hours, with chronic administration yielding longer half-lives, possibly due to saturation of liver binding sites and/or systemic clearance.

53617

Affected cytochrome P450 enzymes:
Cytochrome P450 enzymes involved in the metabolism of propranolol include 2D6, 1A2, and 2C19. Propranolol is also a substrate for the efflux transporter PGP. The aromatic hydroxylation of propranolol to form the active metabolite, 4-hydroxypropranolol, is mediated by CYP2D6. 4-hydroxypropranolol is a substrate and weak inhibitor of CYP2D6. In healthy subjects, no difference in clearance or half-life of propranolol was observed between extensive and poor CYP2D6 metabolizers. In extensive metabolizers, a significant increase in 4-hydroxypropranolol clearance and a significant decrease in the clearance of naphthyloxyactic acid, an inactive metabolite, was noted.

For the treatment of hypertension:

NOTE: The 2007 AHA guidelines for the management of hypertension recommend beta-blockers should only be used as first-line therapy for the treatment of hypertension in patients with angina, prior myocardial infarction, or heart failure.
33826

Oral dosage (immediate-release tablets or oral solution):
Adults: Initially, 40 mg PO twice daily, then increase at 3—7 day intervals up to 160—480 mg/day, given in 2—3 divided doses. Maximum dosage is 640 mg/day.
Elderly: See adult dosage. Begin with conservative initial doses, followed by careful dosage titration. In general, the elderly have unpredictable responses to beta-blockers.
Children†: Initially, 0.5—1 mg/kg/day PO in 4 divided doses. The usual dosage is 1—5 mg/kg/day PO, given in 4 divided doses. Maximum dosage is 8 mg/kg/day.
Oral dosage (extended-release capsules except InnoPran XL):
Adults: Initially, 80 mg PO once daily. Increase dosage at 3—7 day intervals up to 120—160 mg PO once daily. Maximum dosage is 640 mg/day.
Elderly: See adult dosage. Begin with conservative initial doses, followed by careful dosage titration. In general, the elderly have unpredictable responses to beta-blockers.
Children: Safe and effective use has not been established.
Oral dosage (InnoPran XL extended-release capsules only):

Adults: Initially, 80 mg PO once daily at bedtime (approximately 10 PM), taken either on an empty stomach or with food. If needed, increase dosage to 120 mg PO once daily at bedtime. Maximum dosage is 120 mg/day PO; no further BP reduction has been demonstrated at higher doses. Maximal BP response is usually achieved within 2—3 weeks.

Elderly: See adult dosage. Begin with conservative initial doses, followed by careful dosage titration. In general, the elderly have unpredictable responses to beta-blockers.

Children: Safe and effective use has not been established.

Continuous IV infusion dosage† (for patients unable to tolerate oral therapy):

Adults: Limited data suggest a continuous infusion of propranolol may be effective in post-surgical patients who cannot tolerate oral therapy. An infusion rate of 2—3 mg/hr achieved therapeutic propranolol serum levels within 3 hours. Continuous infusions were administered for up to 9 days

Angina Pektoris

No. ICPC II : K74 *Ischaemic herat disease with angina*

No. ICD X : I20.9 *Angina pectoris, unspecified*

Tingkat Kemampuan: 3B

Masalah Kesehatan

Angina pektoris ialah suatu sindrom klinis berupa serangan nyeri dada yang khas, yaitu seperti rasa ditekan atau terasa berat di dada yang sering menjalar ke lengan kiri. Nyeri dada tersebut biasanya timbul pada saat melakukan aktivitas dan segera hilang bila aktivitas dihentikan.

Tingkat kemampuan 3B

Tujuan: mengatasi gejala klinis sampai mendapat pelayanan rawat lanjutan di pelayanan sekunder

Sediaan obat pada layanan primer (Formularium Nasional BPJS 2014):

1	atenolol		
	1.	tab 50 mg	√
2	diltiazem HCl		
	1.	tab 30 mg	√
3	gliseril trinitrat		
	1.	tab sublingual 0,5 mg	√
	2.	kaps SR 2,5 mg	
	3.	kaps SR 5 mg	
	4.	inj 10 mg/mL	
	5.	inj 50 mg/mL	
4	isosorbid dinitrat		
	1.	tab 5 mg	√
	2.	tab 10 mg	
	3.	inj 10 mg/10 mL (i.v.)	
		Untuk kasus rawat inap dan UGD.	

1	asam asetilsalisilat (asetosal)		
	1.	tab 80 mg	√
	2.	tab 100 mg	

Terapi farmakologi:

a. Nitrat dikombinasikan dengan β-blocker atau *Calcium Channel Blocker* (CCB) non dihidropiridin yang tidak meningkatkan *heart rate* (misalnya verapamil, diltiazem). Pemberian dosis pada serangan akut :
   1. Nitrat 10 mg sublingual dapat dilanjutkan dengan 10 mg peroral sampai mendapat pelayanan rawat lanjutan di Pelayanan sekunder.
   2. Beta bloker:
      - Propanolol 20-80 mg dalam dosis terbagi atau
      - Bisoprolol 2,5-5 mg per 24 jam.
   3. *Calcium Channel Blocker (*CCB*)*
      Dipakai bila Beta Blocker merupakan kontraindikasi.
      - Verapamil 80 mg (2-3 kali sehari)
      - Diltiazem 30 mg (3-4 kali sehari)

b. Antipletelet:

Aspirin 160-320 mg sekali minum pada akut.

Atenolol

Description:

Atenolol is a competitive, beta-1-selective adrenergic antagonist, similar to metoprolol. Atenolol has a longer plasma half-life than does metoprolol, which allows for once-daily dosing. Due to its low-lipid solubility, atenolol is renally eliminated, minimally metabolized, and has a lower potential for inducing CNS side effects compared to lipid-soluble beta-blockers (e.g., propranolol). As with other 'cardioselective' beta-blockers, high doses result in attenuated or lost selectivity for the beta-1-receptor. Unlike pindolol, atenolol does not have intrinsic sympathomimetic properties. Atenolol also does not possess membrane-stabilizing activity as pindolol and propranolol do. The 2007 AHA guidelines for the management of hypertension state beta-blockers should not be used as first-line therapy for the treatment of hypertension, as several comparative clinical trials have shown beta blockers to be inferior to ACE inhibitors, angiotensin-receptor blockers, or calcium channel blockers for preventing both stroke and coronary artery disease complications. These guidelines do, however, recommend the use of beta-blockers for the treatment of hypertension in patients with angina, prior myocardial infarction, or heart failure. Atenolol was approved by the FDA in 1981.

Mechanism of Action:

Beta-adrenergic antagonists counter the effect of sympathomimetic neurotransmitters (i.e., catecholamines) by competing for receptor sites. Similar to metoprolol, atenolol, in low doses, selectively blocks sympathetic stimulation mediated by $beta_1$-adrenergic receptors in the heart and vascular smooth muscle. The pharmacodynamic consequences of this activity include: reduction of resting heart rate and, subsequently, cardiac output; reduction of both systolic and diastolic blood pressure at rest and with exercise; and possible reduction of reflex orthostatic hypotension. With higher doses (>100 mg/day), atenolol also competitively blocks $beta_2$-adrenergic responses in the bronchial and vascular smooth muscles. In addition, serum free fatty acid concentrations are decreased and triglyceride levels increased by atenolol.

A critical effect of beta blockade is to provide prophylaxis and reduction in myocardial ischemia and potentially prevent the severity of subsequent myocardial infarction. Part of this effect also may be attributed to the antiarrhythmic properties of beta blockade at the nodal level of

pacemaker control.

Actions that make atenolol useful in treating hypertension include: a negative chronotropic effect that decreases heart rate at rest and after exercise; a negative inotropic effect that decreases cardiac output; reduction of sympathetic outflow from the CNS; and suppression of renin release from the kidneys. Thus, atenolol, like other beta-blockers, affects blood pressure via multiple mechanisms. In general, beta-blockers without intrinsic sympathomimetic activity (ISA) exert detrimental effects on LVH and the lipid profile, and cause sexual dysfunction.

Atenolol is used to treat angina because the drug decreases the oxygen demand of the heart, both by decreasing heart rate and contractility and by lowering blood pressure. However, in patients with cardiac failure, the opposite may be true (i.e., the drug can increase the oxygen demand of the heart.)

Atenolol possesses numerous mechanisms that may contribute to its efficacy in preventing migraine headaches.

Beta-blockade can prevent arterial dilation, inhibit renin secretion, and block catecholamine-induced lipolysis. Blocking lipolysis, decreases arachidonic acid synthesis and subsequent prostaglandin production. Inhibition of platelet aggregation is due to this decrease in prostaglandins and blockade of catecholamine-induced platelet adhesion. Other actions include increased oxygen delivery to tissues and prevention of coagulation during epinephrine release.

Pharmacokinetics:

Atenolol is administered orally and parenterally. Effects on blood pressure do not coincide with effects on heart rate, nor does the antihypertensive effect exhibit a linear dose/pharmacodynamic response. Atenolol is distributed throughout the body and into breast milk. It also crosses the placenta, with fetal serum atenolol concentrations approaching those of the mother. Unlike propranolol, atenolol distribution into the CNS by crossing the blood-brain barrier is minimal. Atenolol is minimally bound to plasma proteins, averaging only 10%, which, along with it low lipophilicity, may explain some of its distribution characteristics. Atenolol undergoes little or no metabolism by the liver, and the absorbed portion is eliminated primarily by renal excretion. Over 85% of an intravenous dose is excreted in urine within 24 hours compared with approximately 50% for an oral dose. The rest of the dose is excreted via the fecal route as unchanged drug. The serum half-life of atenolol in patients with normal renal function

is 6—7 hours in adults.

For the treatment of angina pectoris:

•for the treatment of chronic stable angina:

Oral dosage:
Adults: Initially, 50 mg PO once daily. Increase to 100 mg/day PO if needed after 7 days. Maximum dosage is 200 mg/day PO.
Elderly: See adult dosage; Initiate therapy at the lower end of the adult dosage range (e.g., 25—50 mg PO once daily). Titrate dosage to attain therapeutic goals.

•for the treatment of unstable angina†:
Intravenous-to-oral dosage:
NOTE: Atenolol injection has been discontinued in the US.
Adults: 5 mg IV over 5 min. Repeat 5 mg IV dose in 10 min. If the second dose is tolerated, begin 50 mg PO 10—60 minutes after the second IV dose and then 50 mg PO 12 hours later. Continue oral therapy with 50—100 mg/day PO given in 1—2 divided doses. According to clinical practice guidelines, the intravenous doses can be reserved for high-risk patients and eliminated from the regimen in intermediate- and low-risk patients.

23966

Elderly: See adult IV and PO dosage; Initiate oral therapy at the lower end of the adult dosage range (e.g., 25—50 mg PO once daily). Titrate dosage to attain therapeutic goals.

Diltiazem

Description:

Diltiazem is a benzothiazepine calcium-channel blocking agent that is most similar to verapamil in its clinical use. Diltiazem increases exercise capacity and improves multiple markers of myocardial ischemia. Diltiazem reduces heart rate and blood pressure, may increase cardiac output, improves myocardial perfusion, reduces left ventricular workload, and may reduce coronary vasospasm and ischemia following angioplasty. Diltiazem is used for the management of Prinzmetal's variant angina, stable angina pectoris, unstable angina in patients with preserved left ventricular function,hypertension, paroxysmal supraventricular tachycardia, control of ventricular rate in atrial fibrillation and flutter. It also has been found to possibly reduce recurrent cardiac events, although not mortality, following non-ST-segment elevation myocardial infarction in patients without left ventricular dysfunction;however, this is not an FDA-approved indication at this time. Diltiazem was approved by the FDA for general use in November 1982. Oral diltiazem is marketed in several different dosage forms including regular-release tablets (Cardizem®), twice-daily extended-release capsules (Cardizem® SR), and once-daily extended-release formulations (e.g., Cardizem® CD, Cardizem® LA, Dilacor XR®, Tiazac®, and generic equivalents). The dosage, administration, and approved indications vary with each specific product.

Mechanism of Action:

Diltiazem is similar to verapamil in that it inhibits the influx of extracellular calcium across both the myocardial and vascular smooth muscle cell membranes. Serum calcium levels remain unchanged. Calcium channels in myocardial and vascular smooth muscle cell membranes are selective and allow a slow, inward flow of calcium that contributes to excitation-contraction coupling and electrical discharge (plateau phase of the action potential) of conduction cells in the heart and vasculature. Diltiazem inhibits this influx, possibly by deforming the channel, inhibiting ion-control gating mechanisms, and/or interfering with the release of calcium from the sarcoplasmic reticulum. The resultant decrease in intracellular calcium inhibits the contractile processes of the myocardial smooth muscle cells, resulting in dilation of the coronary and systemic arteries and improved oxygen delivery to the myocardial tissue. In addition, total peripheral resistance, systemic blood pressure, and afterload are decreased. Diltiazem, like verapamil and nifedipine, effectively increases coronary blood flow. Therefore, calcium-channel blockers such as diltiazem are useful in managing angina and hypertension.

The electrophysiologic effects of diltiazem make it a favorable agent for the temporary control of certain supraventricular arrhythmias and for the rapid conversion of paroxysmal supraventricular tachycardias (PSVT) to sinus rhythm.

Diltiazem's inhibitory effects on conduction through the atrioventricular (AV) node is stronger than nifedipine's and similar to verapamil's. This is reflected on the ECG by a prolonged PR interval. Second- or third-degree heart block is possible, especially if diltiazem is given to patients receiving beta-blockers. Resting heart rate also can be decreased, especially in patients with sick sinus syndrome. Its effects on calcium channels in SA and AV nodes, and peripheral vasculature are equipotent. Diltiazem exerts fewer negative inotropic effects than either verapamil or nifedipine. Diltiazem is also less potent as a peripheral vasodilator than nifedipine and related dihydropyridine analogs. In general, calcium-channel blockers exert favorable effects on LVH, and do not worsen insulin resistance or exert detrimental effects on the lipid profile.

Pharmacokinetics:

Diltiazem is administered orally and intravenously. It is widely distributed throughout the body and into maternal breast milk in equal concentrations to those achieved in serum. Roughly 70—80% of the circulating drug is bound to plasma proteins.

About 10—35% of the absorbed dose is metabolized to deacetyldiltiazem, which has 25—50% of the coronary vasodilatory effects of diltiazem. The remaining metabolites are not pharmacologically active. Diltiazem exhibits dose-dependent kinetics, predisposing patients to accumulation with repeated dosing. The half-life ranges from 3.5—9 hours and is usually 4—6 hours. About 2—4% of the drug is excreted unchanged in the urine, with the remainder excreted in the bile and urine.

Affected cytochrome P450 isoenzymes and drug transporter: CYP3A4, P-gp

Diltiazem is an inhibitor, and a substrate, of CYP3A4 and P-gp. It has been postulated that N-demethylated metabolites of diltiazem are potent CYP3A4 inhibitors, and may contribute to the *in vivo* inhibitory effects of diltiazem with repeated dosing. Other drugs that are specific substrates, inhibitors, or inducers of CYP3A4 isoenzymes may interact with diltiazem. Patients taking other drugs that are CYP3A4 substrates, especially patients with renal and/or hepatic impairment, may require dosage adjustment when starting or stopping diltiazem.

For the treatment of chronic stable angina:

Oral dosage (Regular-release tablets):

Adults: Initially, 30 mg PO four times per day administered before meals and at bedtime, gradually increasing the dosage at 1 or 2 day intervals until angina is optimally controlled. Maximum daily dose is 360 mg/day PO, given in 3 or 4 divided doses. The usual dosage range is 180—360 mg/day.

Elderly: See adult dosage. In general, initiate dosage at the lower end of the adult dosage range. Some patients respond to a lower dosage; adjust dosage based on clinical response. In elderly versus younger subjects, the half-life of diltiazem is prolonged and clearance is decreased.

Oral dosage (Extended-release once-daily capsules; includes Cardizem CD, Dilacor XR, Diltia XT capsules, Taztia XT capsules, Tiazac, or generic equivalents):

Adults: Initially, 120—180 mg PO once daily. In general, titrate dosage at 1—2 week intervals. Although there is limited clinical experience with doses greater than 360 mg/day, individual patients may respond to higher doses. Maximum dosage is 480 mg/day PO for Cardizem CD and Dilacor XR; the maximum dosage is listed as up to 540 mg/day PO by the manufacturer for Tiazac.

Elderly: See adult dosage. In general, initiate dosage at the lower end of the adult dosage range. Some patients respond to a lower dosage; adjust dosage based on clinical response. In the elderly versus younger subjects, the half-life of diltiazem is prolonged and clearance is decreased.

Oral dosage (Extended-release once-daily tablets; specifically for Cardizem LA):

Adults: Initially, 180 mg PO once daily, given either in the morning or evening. In general, titrate dosage at 1—2 week intervals. Doses > 360 mg/day do not appear to provide additional benefit. Evening doses up to 420 mg/day (Cardizem LA) have been studied in angina patients.

Elderly: See adult dosage. In general, initiate dosage at the lower end of the adult dosage range. Some patients respond to a lower dosage; adjust dosage based on clinical response. In the elderly versus younger subjects, the half-life of diltiazem is prolonged and clearance is decreased.

For the treatment of variant angina (Prinzmetal's angina):

Oral dosage (Regular-release tablets):

Adults: Initially, 30 mg PO four times per day administered before meals and at bedtime, gradually increasing the dosage at 1 or 2 day intervals until angina is optimally controlled. The usual dosage range is 180—360 mg/day. Maximum daily dose is 480 mg/day, given in 3 or 4 divided doses.

Elderly: See adult dosage. In general, initiate dosage at the lower end of the adult dosage range. Some patients respond to a lower dosage; adjust dosage based on clinical response. In elderly versus younger subjects, the half-life of diltiazem is prolonged and clearance is decreased.

Oral dosage (Extended-release once-daily dosage forms; i.e., Cardizem CD capsules or generic equivalent):

Adults: Initially, 120—180 mg PO once daily. There is limited clinical experience with doses greater than 360 mg/day. Maximum dosage is 540 mg/day PO.

Elderly: See adult dosage. In general, initiate dosage at the lower end of the adult dosage range. Some patients respond to a lower dosage; adjust dosage based on clinical response. In elderly versus younger subjects, the half-life of diltiazem is prolonged and clearance is decreased.

For the relief of ongoing ischemia in patients with unstable angina† or after acute non-ST-segment elevation myocardial infarction† in the absence of congestive heart failure, pulmonary congestion, left ventricular dysfunction, or AV block, when beta-blockers are ineffective or contraindicated:

Oral dosage (Regular-release tablets):

Adults: Initially, 30—60 mg PO four times per day. Dosage may be increased up to 360 mg per day, given in 3—4 divided doses. Individual patients may respond to higher doses up to 480 mg per day.

Elderly: See adult dosage. In general, initiate dosage selection at the lower end of the adult dosage range. Some patients respond to a lower dosage; adjust dosage based on clinical response. In elderly versus younger subjects, the half-life of diltiazem is prolonged and clearance is decreased.

Nitroglycerin

Description:

Nitroglycerin, an organic nitrate available in many dosage forms, is a vasodilator proven to be the mainstay of therapy in the management of angina pectoris. Nitroglycerin is also used to control perioperative hypertension, to produce controlled hypotension during surgical procedures, to treat hypertensive emergencies, and to treat congestive heart failure associated with myocardial infarction. Nitroglycerin has also been used to treat pulmonary hypertension. Synthesized in 1846, nitroglycerin was found to cause severe headaches when placed on the tongue. The drug was later found to exhibit vasodepressor effects similar to those of the drug amyl nitrite, but with less adverse effects and better dosage control. The use of sublingual nitroglycerin for the relief of acute anginal attacks was established in 1879. Because it is inexpensive, has a rapid onset of action, and has a well-documented efficacy, sublingual nitroglycerin is still considered the drug of choice for the acute relief of angina. Although organic nitrates are still frequently prescribed for the relief of angina, they have recently come under scrutiny because of the controversy surrounding claims that nitrate tolerance and attenuation of pharmacodynamic effects have been demonstrated with all nitrate dosage forms. Nitroglycerin was granted FDA approval in 1938. In June 2011, the FDA approved Rectiv, a 0.4% rectal ointment indicated for treatment of pain associated with chronic anal fissures.

45135

Mechanism of Action:

Similar to other nitrites and organic nitrates, nitroglycerin is converted to nitric oxide (NO), a reactive free radical. Nitric oxide, the active intermediate compound common to all agents of this class, activates the enzyme guanylate cyclase, thereby stimulating the synthesis of cyclic guanosine 3',5'-monophosphate (cGMP). This second messenger then activates a series of protein kinase-dependent phosphorylations in the smooth muscle cells, eventually resulting in the dephosphorylation of the myosin light chain of the smooth muscle fiber and the subsequent release, or extrusion, of calcium ions. The contractile state of smooth muscle is normally maintained by a phosphorylated myosin light chain (stimulated by an increase in calcium ions). Thus, the nitrite- or nitrate-induced dephosphorylation of the myosin light chain signals the cell

to release calcium, thereby relaxing the smooth muscle cells and producing vasodilation.

It is believed that nitrates correct myocardial oxygen imbalances by reducing systemic and pulmonary arterial pressure (afterload) and decreasing cardiac output secondary to peripheral dilation rather than coronary artery dilation. Nitrates therefore relax peripheral venous vessels, causing a pooling of venous blood and decreased venous return to the heart, which decreases preload. Nitrates reduce both arterial impedance and venous filling pressures, resulting in a reduction of the left ventricular systolic wall tension, which decreases afterload. Thus, nitrate-induced vasodilation increases venous capacitance and decreases arteriole resistance, thereby reducing both the preload and afterload, and lowering the cardiac oxygen demand.

Total coronary blood flow can be increased by nitrites and nitrates in patients with normal hearts, but in patients with ischemia, nitroglycerin does not increase total coronary blood flow but simply redistributes blood to ischemic areas. This effect is believed to be due to the drug's preferential dilation of the larger conductive vessels of the coronary circulation, which, in the presence of coronary atherosclerosis, redirects the distribution of the coronary blood supply to ischemic areas.

Nitrates cause a transient compensatory increase in heart rate and myocardial contractility that normally would increase myocardial oxygen consumption, yet the nitrate-induced decrease in ventricular wall tension results in a net decrease in myocardial oxygen demand and amelioration of the pain of angina pectoris. In addition, nitroglycerin relaxes all other types of smooth muscle including bronchial, biliary, GI, ureteral, and uterine. Following intra-anal administration of the 0.4% rectal ointment, nitroglycerin reduces anal sphincter tone resulting in decreased resting intra-anal pressure.

Nitrites and nitrates are functional antagonists of acetylcholine, norepinephrine, and histamine.

In individuals who have minimal reflex tachycardia, syncope can result from the decrease in blood pressure that occurs following higher doses of nitrates and nitrites. Although this is not likely to occur with doses of nitrates that do not cause blood pressure reduction, patients should be sitting or lying down during and immediately after administration of several dosage forms of nitroglycerin.

The antihypertensive actions of nitroglycerin are secondary to pharmacologic properties that

make it an effective antianginal agent but are primarily a result of its peripheral vasodilatory effects. With the exception of greater vascular (venous) specificity and the greater variety of pharmaceutical preparations available, nitroglycerin (NTG) is similar to nitroprusside in many respects. Both agents are capable of producing venous (more so with NTG) and arterial dilation, with beneficial effects on redistribution of myocardial blood flow.

Pharmacokinetics:

Nitroglycerin can be administered by the oral, lingual (spray), sublingual, intrabuccal, topical (transdermal), rectal, or intravenous routes. Irrespective of the route of administration, organic nitrates are virtually completely metabolized by the enzyme glutathione-organic nitrate reductase, so the systemic or presystemic hepatic biotransformation is the key determinant of the bioavailability and duration of action of the various preparations. Nitroglycerin distributes widely throughout the body tissues and is approximately 60% plasma protein-bound. The metabolites of nitroglycerin, 1,3- and 1,2-glyceryl dinitrate, are much less potent than the parent compound and have a half-life of approximately 40 minutes, compared to a parent half-life of 1—3 minutes. The metabolites are excreted by the kidneys.

For the treatment of angina:

•for acute angina pectoris or for acute angina pectoris prophylaxis (i.e., situations likely to provoke an anginal attack):

Sublingual dosage:

Adults: 1 tablet (0.3 mg, 0.4 mg, or 0.6 mg strength) SL, dissolved under the tongue or in buccal pouch immediately following indication of anginal attack. During drug administration, the patient should rest, preferably in the sitting position. Symptoms typically improve within 5 minutes. If needed for immediate relief of stable angina symptoms, SL nitroglycerin may be repeated every 5 minutes as needed, up to 3 doses.

Although the traditional recommendation is for patients to take up to 3 SL nitroglycerin doses over 15 minutes before accessing the emergency system, recent guidelines suggest an alternative strategy to reduce delays in emergency care.

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The 2004 ACC/AHA STEMI myocardial infarction guidelines recommend instructing a patient with a prior prescription for nitroglycerin to call 9-1-1 immediately if chest discomfort/pain is persistent or worsened 5 minutes after ONE dose of nitroglycerin.

Self-treatment with nitrates has been identified as a factor resulting in delaying access to emergency care for patients with STEMI, including those with a history of MI or angina.

The STEMI guidelines also note that for patients known to have frequent angina, physicians may provide individualized instructions for the use of SL nitroglycerin, based on the characteristics of the patient's angina, time course, and response to treatment.

The guidelines stress the importance of preventing delays in emergency evaluation due to self-medication.
Geriatric: Consider initiating therapy at the lower end of the adult dosage range (see adult dosage). Elderly patients may be more sensitive to hypotensive and bradycardic effects of nitroglycerin.
Lingual Spray or Aerosol (e.g., Nitrolingual, NitroMist):
Adults: Spray 1—2 metered doses (400—800 mcg) SL, under the tongue. This dose may be repeated every 5 minutes up to a maximum of 3 doses (1200 mcg) given in a 15 minute period. Symptoms typically improve within 5 minutes. If needed for immediate relief of stable angina symptoms, lingual nitroglycerin spray may be repeated every 5 minutes as needed, up to 3 doses.

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•for chronic angina pectoris:

NOTE: A nitrate-free interval is necessary to avoid the development of drug tolerance; although a minimum interval has not been clearly established, 10—12 hours/day has been sufficient with other nitroglycerin formulations.

Oral dosage (extended release capsules):
Adults: Initially, 2.5—6.5 mg PO three to four times daily; titrate to clinical response and adverse reactions as needed. Doses as high as 26 mg four times daily have been used in clinical trials.

Infark Miokard

No. ICPC II : K75 *Acute Myocardial Infarction*
No. ICD X : I21.9 *Acute Myocardial Infarction, Unspecified*

Tingkat Kemampuan: 3B

Masalah Kesehatan

Infark miokard (IM) adalah perkembangan yang cepat dari nekrosis otot jantung yang disebabkan oleh ketidakseimbangan yang kritis antara suplai oksigen dan kebutuhan miokardium. Ini biasanya merupakan hasil dari ruptur plak dengan trombus dalam pembuluh darah koroner, mengakibatkan kekurangan suplai darah ke miokardium.

Penatalaksanaan

Tata Laksana: Segera rujuk setelah pemberian MONACO:

M : Morfin, 2,5-5 mg IV
O : Oksigen 2-4 L/m
N : Nitrat, bisa diberikan nitrogliserin infus dengan dosis mulai dari 5mcg/m (titrasi) atau ISDN 5-10 mg sublingual maksimal 3 kali
A : Aspirin, dosis awal 160-320 mg dilanjutkan dosis pemeliharaan 1 x 160 mg
CO : Clopidogrel, dosis awal 300-600 mg, dilanjutkan dosis pemeliharaan 1 x 75 mg

Obat yang tersedia di puskesmas

Nitrogliserin

ISDN

Aspirin

Takikardia

No. ICPC II : K79 *Paroxysmal Tachicardy*
No. ICD X : R00.0 *Tachicardy Unspecified* I47.1 *Supraventicular Tachicardy* I47.2 *Ventricular Tachicardy*

Tingkat Kemampuan: 3B

Masalah esehatan

Takikardi adalah suatu kondisi dimana denyut jantung istirahat seseorang secara abnormal lebih dari 100 kali per menit.

Sedangkan Supraventikular Takikardi (SVT) adalah takikardi yang berasal dari sumber di atas ventrikel (atrium), dengan ciri gelombang QRS sempit(< 0,12ms) dan frekuensi lebih dari 150 kali per menit.

Ventrikular Takikardi (VT) adalah takikardi yang berasal dari ventrikel, dengan ciri gelombang QRS lebar (> 0,12ms) dan frekuensi biasanya lebih dari 150 kali per menit. VT ini bisa menimbulkan gangguan hemodinamik yang segera memerlukan tindakan resusitasi.

Tata Laksana:

Keadaan ini merupakan keadaan yang mengancam jiwa terutama bila disertai hemodinamik yang tidak stabil. Bila hemodinamik tidak stabil (Tekanan Darah Sistolik < 90 mmHg) dengan nadi melemah, apalagi disertai penurunan kesadaran bahkan pasien menjadi tidak responsif harus dilakukan kardioversi baik dengan obat maupun elektrik. Kondisi ini harus segera dirujuk dengan terpasang infus dan resusitasi jantung paru bila tidak responsif. Oksigen diberikan dengan sungkup O_2 10-15 lpm. Pada kondisi stabil, SVT dapat diatasi dengan dilakukan vagal manuver (memijat A. Karotis atau bola mata selama 10-15 menit). Bila tidak respon, dilanjutkan dengan pemberian adenosin 6 mg bolus cepat. Bila tidak respon boleh diulang dengan 12 mg sebanyak dua kali. Bila tidak respon atau adenosin tidak tersedia, segera rujuk ke layanan sekunder. Pada VT, segera rujuk dengan terpasang infus dan oksigen O_2 nasal 4 l/m.

Obat yang tersedia di layanan primer

amiodaron		Primer		
1.	tab 200 mg		√	√
2.	inj 150 mg/3 mL		√	√
	Untuk kasus rawat inap.			
digoksin				
1.	tab 0,25 mg	√	√	√
2.	inj 0,25 mg/mL		√	√
diltiazem HCl				
1.	inj 5 mg/5 mL		√	√
lidokain				
1.	inj 100 mg, vial (i.v.)		√	√
propranolol				
1.	tab 10 mg	√	√	√
	Untuk kasus-kasus dengan gangguan tiroid.			
2.	inj 1 mg/mL (i.v.)		√	√
	Hanya untuk krisis tiroid atau aritmia dengan palpitasi berlebihan.			

Digoxin

Digitek | Digoxin Elixir | Lanoxicaps | Lanoxin

Drug Information Provided By Gold Standard

Description:

Digoxin is a cardiac glycoside similar to digitoxin, although the pharmacokinetic profiles differ between the two drugs. The ancient Egyptians used cardiac glycosides as a poison, and the Romans used them as a cardiovascular tonic. In 1785, Withering published his famous book on foxglove (i.e., digitalis purpurea) and its uses. Digoxin is indicated for the treatment of congestive heart failure and to control ventricular rate in patients with atrial fibrillation. The use of digoxin to control ventricular rate in patients with chronic atrial fibrillation has declined in recent years; its use is being replaced by more effective rate control agents such as calcium channel blockers While digoxin increases left ventricular ejection fraction, improves symptoms,

and reduces the need for hospitalization in patients with systolic heart failure, overall mortality is not affected.

Although digoxin has been used for decades in patients with heart failure (HF), ACE inhibitors have replaced digoxin as first line therapy for HF due to systolic dysfunction, but digoxin continues to be used as adjunctive therapy for heart failure. When used to treat patients with diastolic heart failure (HF with normal ejection fraction) and normal sinus rhythm who were also receiving ACE inhibitors, digoxin is not associated with a benefit on overall mortality or cardiovascular morbidity.

In patients with atrial fibrillation or atrial flutter, calcium-channel blockers, such as verapamil and diltiazem, are generally more effective than digoxin for controlling ventricular rate. Although digoxin is used for the treatment and/or prophylaxis of supraventricular arrhythmias due to reentry mechanisms, calcium antagonists are generally preferred. The first commercially available digoxin products approved by the FDA went on the market in 1952.

Mechanism of Action:

Digoxin inhibits the Na-K-ATPase membrane pump. Na-K-ATPase regulates intracellular sodium and potassium. Inhibition of this enzyme leads to an increase in intracellular sodium concentration (i.e., decreased outward transport) and ultimately to an increase in intracellular calcium as sodium-calcium exchange is stimulated by high intracellular sodium concentrations. It is believed that increased intracellular concentrations of calcium allow for greater activation of contractile proteins (e.g., actin, myosin). While the contractile proteins and the troponin-tropomysin system are directly involved in muscular contraction, it is not clear how digoxin augments their action. Digoxin does not directly affect these proteins or the cellular mechanisms that provide energy for contraction, nor does it affect contraction in skeletal muscle. Digoxin also increases sympathetic tone, however, this does not account for the positive inotropic effect which persists even in the presence of beta-adrenergic blockade.

Digoxin directly increases the force and velocity of myocardial contraction in both healthy and failing hearts. In the failing heart, an increased force of contraction raises cardiac output, resulting in greater systolic emptying and a smaller diastolic heart size. End-diastolic pressures decrease, leading to a reduction in pulmonary and systemic venous pressures. In patients with normal hearts, however, cardiac output remains unchanged. Digoxin also possesses direct vasoconstrictive properties and reflex CNS-mediated peripheral vasoconstriction. Although this increases vascular resistance, in patients with failing hearts, increased myocardial contractility

predominates and total peripheral resistance drops. In patients with congestive heart failure, an increased cardiac output will decrease sympathetic tone, thereby reducing the heart rate and causing diuresis in edematous patients and improving coronary blood flow.

In addition to its inotropic effects, digoxin also possesses significant actions on the electrical activity of the heart. It increases the slope of phase 4 depolarization, shortens the action potential duration, and decreases the maximal diastolic potential. The increase in vagal activity mediated by cardiac glycosides decreases conduction velocity through the atrioventricular (AV) node, prolonging its effective refractory period. In atrial flutter or fibrillation, digoxin decreases the number of atrial depolarizations that reach the ventricle, thereby slowing ventricular rate. Sympathetic stimulation, however, easily overrides the beneficial inhibitory effects of digoxin on AV nodal conduction. Thus, verapamil and diltiazem are gradually replacing digoxin as the agent to control ventricular rate in atrial tachyarrhythmias. While digoxin is somewhat effective in controlling ventricular rate in atrial fibrillation, it appears to be no better than placebo for converting recent-onset atrial fibrillation to normal sinus rhythm.

Pharmacokinetics:

Digoxin is administered orally, intravenously, or intramuscularly. It distributes throughout the body tissues, with the highest concentrations found in the heart, kidneys, intestine, liver, stomach, and skeletal muscle. Small amounts can be found in the brain. The presence of congestive heart failure slows the rate at which steady-state distribution is achieved. Only 20—30% of the drug is plasma protein-bound. Digoxin crosses the placenta, and maternal and fetal plasma concentrations of the drug are equal.

A small amount of digoxin is metabolized in the liver to inactive metabolites. Thirty to fifty percent of a dose is excreted unchanged in the urine. The elimination half-life in adults is normally 30—40 hours, but heart failure or renal impairment can prolong digoxin elimination.