SN Chugh

2nd Edition

BEDSIDE MEDICINE

Without Tears







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Contents

UNIT 1: CLINICAL CASE DISCUSSION

LONG CASES

Respiratory Diseases 2
1. Chronic Obstructive Pulmonary Disease (COPD) with or without Cor Pulmonale 2
2. Consolidation of the Lung 10
3. Pleural Effusion and Empyema Thoracis 17
4. Pneumothorax 23
5. Hydropneumothorax 28
6. Collapse of the Lung 31
7. Diffuse Fibrosing Alveolitis 34
8. Cavity with Fibrosis 37
9. Pulmonary Tuberculosis 41
10. Bronchial Asthama 45
11. Bronchiectasis 50

Gastrointestinal and Hepatobiliary Diseases 53
12. Jaundice 53
13. Ascites 60
14. Hepatomegaly 66
15. Portal Hypertension 71
16. Chronic Diarrhea and Malabsorption 77

Renal Diseases 83
17. Acute Nephritic Syndrome 83
18. Nephrotic Syndrome 86

Blood Disorders 90
19. Anemia 90
20. Leukemia 95
21. Lymphadenopathy 100
22. Splenomegaly 104
23. Hepatosplenomegaly 108

Endocrine Disorders 112
24. Thyrotoxicosis 112
25. Hypothyroidism 116
26. Diabetes Mellitus 120

Cardiovascular Disorders 131
27. Aortic Stenosis 131
28. Aortic Regurgitation 135
29. Mitral Stenosis 139
30. Mitral Regurgitation 145

31. Infective Endocarditis 152
32. Cor Pulmonale 156
33. Chest Pain 161
34. Dilated Cardiomyopathy 165
Neurological Disorders 168
35. Hemiplegia 168
36. Paraplegia 176
37. Cauda Equina Syndrome 183
38. Peripheral Neuropathy 185

SHORT CASES AND SPOT CASES

Respiratory Diseases 193
39. Deep Vein Thrombosis—Swollen Legs 193
Endocrinal Diseases 196
40. Cushing's Syndrome 196
41. Addison's Disease 200
42. Tetany 203
43. Acromegaly 207
44. Dwarfism 210
45. Tall Stature 214
46. Gynecomastia 218
47. Hirsutism 220
48. Goiter 222
49. Multinodular Goiter 226
Neurological Diseases 229
50. Bell's Palsy 229
51. Third Nerve Palsy vs Horner's Syndrome 232
52. Sixth Cranial Nerve Palsy 235
53. Hydrocephalus and Raised Intracranial Pressure 237
54. Parkinsonism 240
55. Chorea 244
56. Cerebellar Ataxia 247
57. Myotonia 251
58. Myopathy 254
59. Wasting of Small Muscles of Hand and Claw Hands 258
60. Myasthenia Gravis 261
61. Postpolio Paralysis 264
62. Grand Mal Seizures 267
Skin Diseases 270
63. Alopecia 270
64. Erythema Nodosum 273
65. Hyperpigmentation 275
66. Leprosy 277
67. Raynaud's Phenomenon 282
68. Subcutaneous Swellings/Masses 287

69. Scabies 291
70. Psoriasis 293
71. Pityriasis Versicolor (Tinea Versicolor) 296
72. Systemic Lupus Erythematosus 298
Blood Disorders 302
73. Thombocytopenia 302
Cardiovascular Disorders 306
74. Cyanotic Congenital Heart Disease 306
75. Superior Mediastinal Compression 309
76. Pericarditis with Effusion 311
77. Ventricular Septal Defect 314
78. Systemic Hypertension 316
Rheumatological Diseases 319
79. Polyarthritis 319
Renal Diseases 323
80. Adult Polycystic Kidney Disease 323
Gastrointestinal Diseases 326
81. Abdominal Mass 326

UNIT 2: BEDSIDE PROCEDURES AND INSTRUMENTS

Bedside Procedures 330
- Lumbar Puncture 330
- Bone Marrow Aspiration 332
- Tissue Biopsy Needle 332
- Aspiration (Paracentesis) 334
- Tracheostomy 334
- Endotracheal Intubation 335
- Nasogastric (Ryle's Tube) Intubation 335
- Urinary Catheterization 336

Bedside Instruments 337
- Oxygen Delivery Devices 337
- Nasopharyngeal Suction Catheter 338
- Intravenous Line Access (IV Access) 338
- Intravenous Infusion Set 339
- Stomach (Gastric) Lavage Tube 340
- Insulin Delivery Devices 340
- Hypodermic (Tuberculin) Syringe 341
- Ordinary Syringes 341
- Metered dose Inhaler 341
- Spacehaler 342
- Nebulizer 343
- Ambu Bag 343
- Three Way 343
- Clinical Thermometer 344

UNIT 3: COMMONLY USED DRUGS

Drugs Used in Cardiology **346**
Drugs Used in CNS and Psychiatry **366**
Drugs Used in Gastroenterology **379**
Hormones **384**
Infections, Infestations and Vaccination **399**
Nutrition **420**
Drugs Used in Respiratory Diseases **426**

UNIT 4: RADIOLOGY

X-ray Chest (Normal and Abnormal) **432**
- Acute Pulmonary Edema 434
- Pulmonary embolism 435
- Homogenous Opacity Involving one Hemithorax 435
- Coin-shaped Shadow 436
- Cavitatory Lung Lesion 437
- Ring Shadows 438
- Reticulonodular/Miliary Shadows 439
- Calcification in the Lung Fields 441
- The Black (Hypertranslucent) Lung Fields 443
- The Abnormalities of the Subdiaphragmatic Region and the Diaphragm 444
- Hilar Enlargement (Widening of the Hilum) 445
- Abnormal Heart Shadow 448

Abdominal X-ray (Normal and Abnormal) **451**
- Abnormalities of Spine X-ray Film 453
- Abnormally Placed Kidney 455
- The Hollow Organs 455
- Sigmoid Volvulus 457
- Calcification of Abdomen 457

Contrast Studies **460**
- Barium Study 460
- Intravenous Pyelography 462

Index *465*

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Commonly Used Drugs



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Drugs Used in Cardiology

CARDIOVASCULAR DRUGS

Categorization of drugs used in disorders of cardiovascular system is:

CARDIAC STIMULANT

a. Cardiac stimulants, e.g. glycosides, (digoxin, digitoxin, anabine) and amrinone (inamrinone). They are discussed in Table 3.1.
b. Sympathomimetic amines, e.g. noradrenaline, adrenaline, isoproterenol (isoprenaline), dopamine and dobutamine. They have been dealt separately.

ANTIARRHYTHMIC DRUGS (VAUGHAN WILLIAM CLASSIFICATION (TABLE 3.2)

Class I (Block Na Channels)

1A: Drugs that reduce Vmax and prolong action potential duration

- Quinidine
- Procainamide
- Disopyramide

1B: Drugs that do not reduce Vmax but prolong action potential duration

- Mexiletine
- Lidocaine
- Phenytoin
- Tocainide

1C: Drugs that reduce Vmax, primarily slow conduction and can prolong refractoriness

- Flecainide
- Propafenone
- Moricizine

Class II: Beta blockers (block beta-adrenergic receptors)

- Propranolol, metoprolol, alenolol, timolol, oxypre-nolol, sotalol, bisoprolol, nebivolol, carvedilol

Class III: Drugs block potassium channels and block multiple phases of the action potential and prolong repolarization

- Amiodarone, sotalol, bretylium and N-acetylpro-cainamide, ibutilide, dofetilide

Class IV: Calcium channel blockers

- Diltiazem, verapamil and others

Other antiarrhythmic drugs

- Adenosine
- Digitalis

BETA BLOCKERS

Beta receptors can be separated into two categories; (i) that affect the heart (β1) and (ii) that affect predominantly blood vessels (β2) or the bronchi. Therefore β1 receptors produce cardiac stimulation and β2 receptors produce bronchodilation and vasodilation. Cardioselective β1 blockers antagonise the β1-cardiostimulatory effects and have less effect on β2-responses. Nonselective-beta blockers antagonise the effects of both β1 and β2 receptors. At high doses, even selective beta blockers also block β2 receptors.

Some beta blockers (alprenolol, oxyprenolol, pindolol) possess "intrinsic sympathomimetic activity" i.e. they slightly activate the β-receptors. These drugs are as efficacious as other beta blockers without intrinsic sympathomimetic activity and may cause less slowing of heart rate, less prolongation of AV conduction. They have been shown to produce less depression of LV functions than beta blockers without intrinsic sympathomimetic effect.

Only nonselective beta blockers without intrinsic sympathomimetic activity have been demonstrated to reduce mortality in patients with myocardial infarction.

Classification

Base on cardioselectivity and vasodilatory effect, they are classified into 4 groups (Fig 3.1).

Actions

1. *Antihypertensive*: Both selective and nonselective beta blockers antagonise the sympathetic effects on the heart, thus, lower cardiac output and arterial pressure. Metoprolol and atenolol, both cardioselective beta blockers are preferred as antihypertensives.
2. *Antianginal effect*: Both cardioselective and nonselective beta blockers are used in treatment of angina (stable, unstable and postmyocardial) because they reduce myocardial respsonse to sympathetic stimulation and decrease myocardial O_2 demand.
3. *Antiarrhythmic effect*: All beta blockers are classified class II antiarrhythmics except sotalol (has both class II and III effects). They are used in a variety of cardiac arrhythmias, e.g. sinus tachycardia, anxiety neurosis with tachycardia, atrial flutter, atrial fibrillation, paroxysmal atrial tachycardia and ventricular arrhythmias. The antiarrhythmic effects is achieved by blockade of β_1 receptors in the myocardium rather than quinidine like effect (some beta blockers exert local anesthetic and quinidine like effect). They delay conduction through AV node, hence, reduce heart rate response in atrial fibrillation or PSVT.

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Table 3.1: Cardiac stimulants

Drugs	Mechanism of action	Uses	Doses	Side effects	Special remarks
1. *Cardiac stimulants*					
Digoxin	• Positive inotropic effect in normal, nonfailing hypertrophied and failing hearts • Negative chronotropic effect (slows conduction through AV node by increasing effective refractory period by an enhanced vagal effect) • It enhances excitability, automaticity and ectopic impulse formation	• CHF • To slow the ventricular response in atrial fibrillation and atrial flutter • To terminate PSVT	Oral: Loading dose 0.25-0.5 mg stat then 0.25 mg every 4 hr × 2 doses Maintenance dose (0.25 mg on alternate days or 5 days in a week) IV Loading dose: 0.25-0.5 mg slow IV bolus, then 0.25 mg IV after 2-4 hours, then followed by oral drug.	1. *Early:* Anorexia, nausea, vomiting due to effect of drug on medullary centres. • Cardiac e.g. VPCs, bigeminy rhythm, nonparoxysmal SVT with block (Wenckebach) ventricular tachycardia, ventricular fibrillation • Sinus arrhythmias, (sinus arrest, SA blocks), AV junctional and multifocal or bidirectional VT 2. Chronic intoxication • Exacerbation of heart failure, weight loss, cachexia, neuralgias, gynecomastia, yellow vision, delirium	• Avoid administration within 2 hours of antacid • May be proarrhythmic • Monitor K^+ and correct hypovolumia • Its serum level increase with verapamil, quinidine and amiodarone • For digitalis induced arrhythmias use phenytoin, or a betablocker or lidocaine • Fab antibodies are used for severe intoxication
Amrinone	• Positive inotropic effect (increases CO), vasodilator agent (decreases preload and afterload)	Short-term management of CHF in patients unresponsive to digitalis, diuretics and vasodilators	IV Loading dose: 0.75 mg/kg over 2-3 min, may be repeated after 30 min Maintenance infusion 5-15 mg/kg/min (dose titrated according to response). Do not exceed 10 mg/kg in a day	• GI tract symptoms, e.g. nausea, vomiting, pain abdomen, anorexia • Cardiac symptoms, hypotension, tachycardia arrhythmias • Hepatotoxicity (jaundice) • Hypersensitivity reactions e.g. pericarditis, pleuritus, myositis, vasculitis, ascites • Lungs: nodular pulmonary shadows, hypoxemia, cough, fever, chest pain	• Avoid mixing in dextrose • Incompatible with furosemide • May exacerbate myocardial ischemia or worsen ventricular ectopy

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Table 3.2: Antiarrhythmic drugs

Drugs	Mechanism of action	Uses	Doses	Side effects	Remarks
CLASS I	**BLOCK NA^+ CHANNELS**				
1A.	**Reduce V_{max} and prolong action potential duration**				
• Quinidine	—do—	VT and SVT; APC/VPC 6-8 hr daily orally PSVT, atrial fibrillation	200-300 mg • Nausea, vomiting, diarrhea 400-600 mg every 2-3 hourly until reverted then 200-300 mg 6-8 hourly	• Hepatitis, cardiac toxicity • Monitor blood, liver, kidney abdominal pain, dizziness sweating, headache • Hemolytic anemia agranulocytosis, thrombo-cytopenic purpura • Bradycardia, hypotension • Allergy, rash, angioneurotic edema, flushing • Cinchonism, e.g. impaired hearing	• Monitor for GI distress functions • Monitor ECG and serum levels • Contraindications are acute infection, AV block, myocarditis, cardiac insufficiency, thrombo-cytopenia, prolong Q-T syndrome, myasthenia, digitalis toxicity, pregnancy
• Procainamide	—do—	—do— Cardiac arrhythmias associated with anesthesia, surgery	250-1000 mg every 3-6 hourly IM until oral therapy possible		• Same as above • May induce lupus syndrome
1. B.	**Do not reduce V_{max}, shorten action potential duration**				
• Mexiletine	—do—	Ventricular arrhythmias	200-400 mg tid upto upto 1200 mg/day/oral IV 200-250 mg IV infusion at a rate of 1 mg/min	• Nausea, vomiting, constipation • Bradycardia, hypotension • Confusion, convulsions ataxia and CNS disturbance • Hepatitis, blood dyscrasias	• Monitor ECG and BP • Proarrhythmic drug may induce torsades de pointes
• Phenytoin	—do—	• Digital induced ventricular arrhythmias • As an antiepileptic • For neuropathic pains e.g. trigeminal neuralgia, diabetic neuropathy	Oral: 100 mg bid or tid IV: Dilantinisation 500-1000 mg as IV drip followed by 100 mg tid orally or IV	Read side effects in antiepileptic drugs	• Read antiepileptics
• Lidocaine	—do—	Ventricular arrhythmias	Loading dose: 1-1.5 mg/kg IV push, may be repeated as 0.5-1.5 mg/kg IV after 5-15 minutes followed by drip	• Nervousness, dizziness blurred vision, tremors numbness, tinnitis, nausea vomiting • Bradycardia, hypotension cardiovascular collapse	• BP monitoring and ECG control essential • Bradycardia, AV blocks and cardiac decompen-sation are its contraindications

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Drugs	Mechanism of action	Uses	Doses	Side effects	Remarks
1. C	**Reduce V_{max} primarily, slow conduction and can prolong refractoriness**				
• Flecainide • Encainide • Propafenone	—do— —do— —do—	Supraventricular and Ventricular arrhythmias e.g. VT	• 50-100 mg 12 hourly orally • 25-50 mg 8 hourly orally • 150 mg tid orally (upto 300 mg tid)		• Monitor ECG • May be proarrhythmic
CLASS II	**BETA BLOCKERS**	**Read beta blockers. They are discussed separately**			
CLASS III	**DRUGS BLOCK K^+ CHANNELS, BLOCK MULTIPLE PHASES OF ACTION POTENTIAL AND PROLONG REPOLARISATION**				
• Amiodarone	—do—	• Potentially life threatening ventricular arrhythmias unresponsive to conventional therapy	*Oral:* Loading dose 800 to 1600 mg/day for 1-3 weeks	• Liver toxicity • GI symptoms • Pulmonary fibrosis • Photosensitivity • Hypothyroidism or hyperthyroidism	• Monitor liver and thyroid function • Half-life is 13-107 days • May be proarrhythmic
		• Supraventricular arrhythmias, e.g. AV nodal, AV reentry, junctional tachycardia, atrial flutter and fibrillation	600-800 mg/day for 4 weeks then 400 mg/day **IV for VT:** 15 mg/min as infusion for 10 minutes followed by 1 mg/min for 6 hours for the next several days as necessary	• Disorders of thyroid function e.g. hyper and hypothyroidism • Cardiac toxicity, e.g. bradycardia, ventricular tachyarrhythmias • Neuropathy	• Monitor ECG for bradycardia, prolongation of PR, QRS and QT_C intervals • May increase serum levels of digoxin, class I drugs • High IV dose infusion may cause hypotension
• Bretylium tosylate	—do—	• Life-threatening ventricular arrhythmias unresponsive to conventional drugs • Drug-resistant ventricular tachyarrhythmias	**VF:** 5 mg/kg IV (diluted both 50-100 ml of 5% dextrose) push; if no response, then 10 mg/kg IV push (diluted with 50-100 ml of dextrose) then maintain infusion at 1-2 mg/min (do not exceed 30-35 mg/kg/day)	• Orthostatic hypotension • Nausea, vomiting • Increased salivation and parotid pain	• Rapid IV infusion may cause hypotension • Avoid in digitalis toxicity
• Sotalol	Class II (betablocker) drug but has class III properties also	• Approved only to treat ventricular tachyarrhythmias	Oral: 80 bid to 320 mg/day	• Side effects of beta blockers may occur • Reduce the dose in	• Watch for proarrhythmic effect • Monitor QT interval, renal insufficiency

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Drugs	Mechanism of action	Uses	Doses	Side effects	Remarks
CLASS IV	**CALCIUM CHANNEL BLOCKERS—READ THE TEXT (DISCUSSED SEPARATELY)**				
OTHER ANTIARRHYTHMICS					
• Adenosine	• Slows conduction through AV node, interrupts reentry pathway in AV node • Vasodilator	• Narrow QRS complex paroxysmal supraventricular tachycardia (PSVT) • Used for pharmacological stress testing	IV: 6 mg IV push over 1-3 seconds (follow with 20 ml NS flush), if no response in 1-2 min; then 12 mg rapid IV push	• Flushing; dyspnea, headache, chest pressure • Hypotension • Bradycardia and conduction disturbances	• Can be used to determine origin of wide QRS tachycardia (ineffective in the presence of VT) • Short half-life (<5 sec) • May produce transient bradycardia and ventricular ectopy • Do not use in 2nd and 3 degree AV block or sick sinus syndrome unless pacemaker is *in situ*
• Magnesium	• Hypomagnesemia can precipitate dysarrhythmias and pump failure • Electrolyte plays an important role in initiation and maintenance of cardiac muscle contraction • Membrane stabilising agent and vasodilator	• Refractory life-threatening arrhythmias (VT and VF) not responding to conventional drugs • Torsade de pointes • Post-myocardial infarction arrhythmias • Used for treatment of refractory epilepsy and bronchial asthma	**For refractory VF/VT;** 1-2 g diluted in 100 ml 5% dextrose and infuse over 1-2 min **Post MI:** 1-2 g (8-16 mEq) in 50-100 ml in 5% dextrose and infuse over 5-60 minutes and follow 0.5-1.0 g/hr IV over 24 hr	• Flushing, headache, tachycardia, hypotension	• May cause hypotension or asystole

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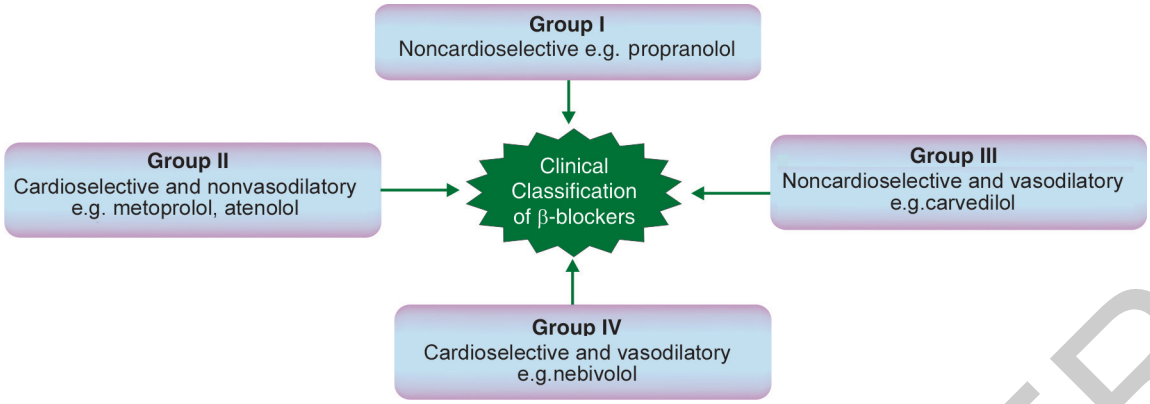

Fig. 3.1: Clinical classification of beta blockers

4. *Antithyroid*: Nonselective beta blockers without intrinsic sympathomimetic activity are used to block the sympathetic stimulation in thyrotoxicosis, hence, are used for relief of thyrotoxic symptoms. In addition, they depress peripheral conversion of T_4 to T_3 and exert mild antithyroid effect.

Uses of beta blockers: They are used in the treatment of:

- Hypertension
- Angina
- Arrhythmias
- Some patients of CHF (e.g. carvidelol)
- Pheochromocytoma
- Mitral valve prolapse
- Anxiety neurosis
- Thyrotoxicosis
- Migrainous headache
- Essential tremors
- Glaucoma (timolol eyedrops)
- Esmolol is the only beta blocker used in the treatment of narrow QRS tachycardia (PSVT).

Drugs and Dosage

Atenolol	Oral: 25-150 mg daily
Metoprolol	25-450 mg in divided doses/day orally IV: Acute MI: 5 mg IV push over 2 min × 3 doses then 50 mg orally every 6 hourly
Propranolol	Oral: 10-80 mg bid or qid upto 320 mg/day IV: 0.5-3.0 mg IV push, may be repeated in 2 min then after every 4 hour
Nadolol	Oral: 40-120 mg/day upto 240 mg
Sotalol	Oral: 80 mg bid upto 320 mg/day
Timolol	Oral: 10-20 mg bid to max of 60 mg
Carvidelol	Oral: 3.75 to 12.5 mg/day
Esmolol	IV infusion: Loading dose 500 mg/kg over 1 minute followed by 50 mg/kg/min infusion over 4 min; may be repeated with increase in maintenance dose at interval of 5 min (do not exceed 200 mg/kg/min)

Adverse Effects

They are due to beta blockade (Box 3.1).

BOX 3.1: ADVERSE EFFECTS OF BETA BLOCKERS

Cardiovascular	*Noncardiovascular*
• Hypotension, bradycardia, AV blocks, precipitation of CHF, cold extremities, • Raynaud's phenomenon	• Bronchospasm • Hypoglycemia • Allergic manifestations • Dizziness, insomnia, vivid dreams, depression, headache, muscle cramps • Nasal stuffiness, tiredness • Vomiting, diarrhea, constipation

Contraindications

- AV blocks
- Gross CHF refractory to digitalis
- Bronchial asthma or allergic conditions
- Cardiogenic shock
- Anesthesia
- Esophageal stricture and/or obstructive changes in GI tract

Special Precaution to be Observed

- Beta blockers should not be stopped abruptly. They should be withdrawn slowly
- They should not be used in CHF unless patient is fully digitalised. Carvidolol and nebivolol are only used in CHF.
- They should be avoided in combination with calcium channel blockers because of their potentiating effects
- Avoid their use in diabetes mellitus as they may mask features of hypoglycemia, if it develops.

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- When used IV, give slowly or with atropine so to avoid severe bradycardia
- Pregnancy safety has not be proved

CALCIUM CHANNEL BLOCKERS

Actions

1. They block slow inward calcium current in all cardiac fibers including SA and AV nodes, thus, reduce the height of action potential, shorten muscle action potential and prolong its duration, hence, are classified as class IV antiarrhythmic.
2. They depress the conduction through AV node. Pacemaker activity of SA node is also depressed.
3. They are vasodilators, hence, reduce the preload, for which they are used in CHF and HT.

Indications (Table 3.3)

Side effects and contraindications/special precaution
See the Box 3.2.

Classification

The WHO has classified Ca^{++} antagonists according to their pharmacological and clinical effects.

Class I (Verapamil) agents, *in vivo*, they have most potent negative inotropic effect. Their depressant effect may precipitate CHF. They cannot be used with beta blocker.

Class II (Nifedipine, nicardipine, amlodipine) agents do not depress conduction or contraction, therefore, the risk of precipitation of CHF is reduced. Therefore, they can be used in combination with beta blockers as they even may reverse some of the negative inotropic effects of beta blockers.

BOX 3.2: CALCIUM CHANNEL BLOCKERS

Side effects

- Dizziness, headache, flushes, fatigue, ankle edema
- Nausea, vomiting, constipation
- Reflex tachycardia
- Allergies
- Gynecomastia
- Gingival hyperplasia
- Reversible liver function impairment
- IV administration may lead to decreased HR, (bradycardia), hypotension, depressed myocardial contractility, (CHF) Rarely 2nd and 3rd degree AV block

Drug Interactions:
Digoxin, beta blockers, anti-arrhythmics, theophylline, carbamazepine, phenytoin, rifampicin, etc.

Contraindications

- Cardiogenic shock
- 2nd and 3rd degree AV block
- Severe bradycardia
- Sick sinus syndrome
- Uncompensated CHF
- Severe LV dysfunction
- Atrial flutter or fibrillation with accessory bypass

Precautions

- Pregnancy, lactation
- Poor cardiac reserve
- First degree AV block, bradycardia, conduction disturbances
- Acute phase of MI
- Concomitant use of beta blockers
- Hepatic and renal impairment

Class III agents (e.g. diltiazem). It has a little or negligible negative inotropic effect. It has a selective effect on coronary arteries with little effect on peripheral vessels, hence, does not cause reflex tachycardia.

ANTIHYPERTENSIVES

Drugs used in the treatment of hypertension according to site of action are tabulated (Table 3.4).

a. Diuretics—Read diuretics
b. Antiadrenergic
   i. Central acting, e.g. clonidine, methyldopa
   ii. Autonomic ganglia, e.g. trimethaphan
   iii. Nerve endings, e.g. reserpine, guanethidine

Table 3.3: Calcium channel blockers—indications, drug and dose

Indications	Drug	Route	Dosage
• Antianginal, coronary spasm (Prinzmetal's angina) • Hypertension • Non-Q wave MI (Non-ST elevation MI) • Control of ventricular rate in supraventricular tachycardia, atrial fibrillation and atrial flutter	Diltiazem:	Oral: IV:	30-120 mg tid or qid 0.25 mg/kg I.V push over 2 min; after 15 min 0.35 mg/kg I.V push over 2 minute
	Verapamil	Oral: IV	40-120 mg tid or qid 2.5-5 mg I.V push over 2 min after 15-30 min may repeat 5-10 mg I.V push over 2 min to a total of 20 mg
• Hypertrophic cardiomyopathy • Vasospastic phenomenon, e.g. Raynaud's phenomenon			
• A combination of Ca^{++} antagonist (nifedipine, amlodipine) with nitrates form an effective combination for treatment of angina with heart failure, sick sinus syndrome or AV conduction disturbance	Nifedipine Sublingual	Oral:	10-40 mg tid or qid upto 160 mg/day 5-10 mg SL to be repeated if necessary
	Amlodipine	Oral:	5-10 mg bid

Note: Nifedipine and amlodipine can only be combined with beta blockers, otherwise combination of diltiazem and verapamil with beta blockers is detrimental

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Table 3.4: Antihypertensive drugs

Site of action	Drug	Dosage	Indications	Contraindication/cautions	Common side effects
Diuretics	Have been discussed separately				
Antiadrenergic drugs					
Central	Clonidine	Oral: 0.05-0.6 mg twice daily	• Mild to moderate hypertension • Hypertension with renal disease	—	Postural hypotension, sedation, dry mouth, impotence, constipation, fluid retention, depression, sleep disturbance, rebound hypertension after abrupt withdrawal
	Methyldopa (also acts by blocking sympathetic nerves)	Oral: 250-1000 mg twice daily I.V: 250-1000 mg 4-6 hourly	• Mild to moderate hypertension • Drug of choice for hypertension in pregnancy • Intravenously used for malignant hypertension	• Pheochromocytoma • Hepatic disease • During MAO inhibitor treatment	Postural hypotension, sedation, fatigue, diarrhea, impaired ejaculation, fever, gynecomastia, lactation, positive Coombs' test, chronic hepatitis, ulcerative colitis, SLE like syndrome
Autonomic ganglia blocker	Trimethaphan	IV: 1-6 mg/min	Severe and malignant hypertension	Severe coronary artery disease, severe cerebrovascular insufficiency, diabetes on hypoglycemic therapy, glaucoma, prostatism	Postural hypotension, visual symptoms, dry mouth, constipation, urinary retention, impotence
Nerve endings, e.g. Adrenolytic	Reserpine	Oral: 0.05-0.25 mg daily	• Mild to moderate hypertension in young • Raynaud's phenomenon	Pheochromocytoma, peptic ulcer, depression, MAO inhibitor therapy	Depression, nightmares, nasal congestion, dyspepsia, diarrhea, impotence
	Guanethidine	Oral: 10-15 mg/day	Moderate to severe hypertension	Pheochromocytoma, coronary artery disease, cerebrovascular insufficiency, MAO inhibitor therapy	Postural hypotension, bradycardia, dry mouth, diarrhea, impaired ejaculation, edema, asthma
	Phentolamine	Oral: 1-5 mg bolus	Suspected or proved pheochromocytoma	Severe coronary artery disease	Tachycardia, weakness, dizziness, flushing
Alpha receptors blocker	Phenoxybenzamine	Oral: 10-50 mg once or twice a day	Proved pheochromocytoma	—	Postural hypotension, miosis, tachycardia, dry mouth, nasal congestion
	Prazosin	Oral: 1-10 mg twice a day	• Mild to moderate hypertension • Raynaud's phenomenon	Use with caution in elderly	Sudden syncope, headache, sedation, dizziness, tachycardia, dry mouth, fluid retention
Beta blockers	Read as already discussed				
Alpha and beta receptor blocker	Labetalol	Oral: 100-600 mg twice a day; IV: 2 mg/min	Similar	Similar	Similar to beta blockers with more postural effects

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Site of action	Drug	Dosage	Indications	Contraindication/cautions	Common side effects
Vasodilators					
Vascular smooth muscle	Hydralazine	Oral: 10-75 mg 4 times a day	As an adjuvant to treatment of moderate to severe hypertension	Lupus erythematosus (SLE), severe coronary artery disease	Headache, tachycardia, angina, nausea, anorexia, vomiting, diarrhea, SLE syndrome, rash, edema
	Minoxidil	Oral: 2.5-40 mg twice a day	Severe hypertension	Severe coronary artery disease	Tachycardia, aggravation of angina, fluid retention, hair growth (hypertrichosis), coarsening of facial features, pericardial effusion
	Diazoxide	IV 1-3 mg/kg upto 150 mg rapidly	Severe to malignant hypertension	Diabetes, hyperuricemia, CHF	Hyperglycemia, hyperuricemia, fluid retention
	Nitroprusside	IV: 0.5-8 (mg/kg/min)	Malignant hypertension		apprehension, weakness, nausea, vomiting, diaphoresis, muscle twitching, cyanide toxicity
Calcium Channel Blockers	Read as already discussed				
Angiotensin Converting Enzyme (ACE) Inhibitors					
The drugs by blocking the ACE, suppress the angiotensin II formation, thus, affect primarily renin-angiotensin aldosterone system	Captopril	Oral: 12.5-75 mg twice a day	• Mild to moderate hypertension • Renal artery stenosis (unilateral) • CHF refractory to digoxin and diuretics • Hypertension with renal failure (S. creatinine < 3.5 mg%) • Nephrotic syndrome to reduce albuminuria	• Renal failure (reduce the dose) • Bilateral renal artery stenosis • Pregnancy	Leukopenia, pancytopenia, hypotension, angiedema, cough, urticarial rash, fever, loss of taste, acute renal failure in bilateral renal artery stenosis, hyperkalemia
	Enalapril	Oral: 2.5-40 mg/day			Same as captopril, but cough and angiedema can be more frequent. All are given once daily dose but side-effects are reduced if given twice a day
	Benazepril	Oral: 10-40 mg/day			
	Fosinopril	Oral: 10-40 mg/day			
	Lisnopril	Oral: 5-40 mg/day			
	Ramipril	Oral: 2.5-20 mg/day			
	Perindopril	Oral: 2-4 mg/day			
Angiotensin Receptor Blockers (ARBs)					
They block angiotensin receptors	Losartan	Oral: 25-50 mg once or twice/day	• Mild to moderate hypertension • Renal hypertension • Diabetic nephropathy with hypertension	• Pregnancy • Bilateral renal artery stenosis	• Hypotension, acute renal failure in bilateral renal artery stenosis, hyperkalemia
	Irbesartan	Oral: 150-300 mg once or twice/day			

Note: Previously adopted step-ladder pattern of treatment for hypertension is obsolete nowadays. The drug is chosen depending on the situation. Initially, monotherapy is instituted in all grades of hypertension, substituted by polytherapy depending on the severity of hypertension, specific situation and response to treatment. Diuretics and betablockers/calcium channel blockers are preferred for initial therapy.

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iv. Alpha blockers, e.g. phentolamine, phenoxybenzamine, prazosin
v. Beta blockers
vi. Alpha/beta blockers, e.g. labetalol

c. Vasodilators: Vascular smooth muscle relaxants, e.g. hydralazine, minoxidil, diazoxide, nitroprusside
d. Angiotensin converting enzyme inhibitors (ACE inhibitors): They include; captopril, enalapril, benasepril, fosinopril, lisinopril and ramipril
e. Angiotensin receptors blockers: They include losartan, irbesartan, candesartan
f. Calcium channel blockers: They include, nifedipine amlodipine, felodipine, nicardipine, diltiazem, verapamil

Choice of Antihypertensive during Pregnancy

The safety of antihypertensive during pregnancy is depicted in Table 3.5.

Hypertension in Elderly

Antihypertensive therapy reduces the incidence of cardiovascular complications. This benefit is evident upto 85 years of age. The criteria for treatment include diastolic blood pressure ≥100 mm Hg or systolic ≥160 mm Hg over 3 to 6 months observation. A low dose of thiazide is the first drug of choice with addition of a beta blocker when required.

Antihypertensive Drug Choices in Specific Situations (Table 3.6)

ANTIANGINAL DRUGS

Angina can be stable (due to atheromatous plaques in the coronary artery) or unstable (due to plaque rupture) It is important to differentiate between the two. The antianginal drugs include;

Table 3.5: Safety of antihypertensive during pregnancy

Class of drug	Safety	Recommendation
Methyldopa	Safe	Treatment of choice
Beta blockers	Limited experience in first trimester. Use in late pregnancy can cause neonatal hypoglycemia and bradycardia	Avoid in first trimester, if possible
Calcium channel blockers	Limited experience	Second-line treatment
Diuretics	Theoretical risk of compromising uteroplacental blood flow	Avoid
ACE inhibitors	Serious problems in the fetus may occur such as oligohydramnios and renal dysfunction, especially after exposure in 2nd and 3rd trimesters	Contraindicated

Note:
1. In the second and third trimesters, antihypertensive agents are not indicated unless the diastolic pressure exceeds 95 mm of Hg.
2. Hypertensive female becoming pregnant and pregnancy with hypertension (pregnancy-induced hypertension, eclampsia, pre-eclampsia) are different terms but treatment remains same.

Table 3.6: Choice of antihypertensive in specific conditions

Condition	Preferred	Alternative/avoid
Diabetes mellitus	• ACE-inhibitor • ARB (angiotensin receptor blocker) • Calcium antagonist	• Avoid thiazide diuretic • Avoid betablockers
Hyperlipidemia	α_1-antagonist	• ACE inhibitor • Calcium antagonist • Avoid diuretic and beta blockers
Angina	• Beta blockers • Calcium antagonist	
Heart failure	ACE inhibitor	Diuretics and α_1-antagonists
Asthma	—do—	Avoid beta blockers
Peripheral vascular disease	Calcium antagonist	α_1-antagonist, avoid beta blockers
Elderly patients	Low dose thiazide and/or a calcium channel blocker	

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1. Nitrates
2. Beta blockers (already discussed)
3. Calcium channel blockers (already discussed)
4. Potassium channel activators

Most patients of angina pectoris are usually treated with beta blockers or calcium channel blockers. However, short-acting nitrates can play an important role both as prophylactic (drug to be taken before exertion) and during acute chest pain occurring at rest or exertion. Nitrates are also used as sole therapy in elderly patients with infrequent attacks.

Nitrates

Actions

1. Their precise mechanism of action is unknown but appears to depend on their conversion to the nitrate ion which is considered to generate oxide. This is possibly the same molecule as "endothelial derived relaxation factor (EDRF), the endogenous nitrate" responsible for vasodilation in hypoxia. Therefore, the predominant effect of nitrates is vasodilation of the venous capacitance vessels (reduction of preload on the heart). This reduction of preload reduces the pressure in the ventricles which, in turn, reduces wall tension, hence, reduces myocardial O_2 demand. They also dilate arteriolar vessels, thus, also reduce afterload on the heart with the result the amount of work of the heart is reduced.
2. In addition, they may increase coronary blood flow (a little effect), but they appear to redistribute blood to ischemic areas particularly the subendocardial regions which are subject to the greatest amount of pressure during systole.

   By both these actions, they relieve angina both exertional and vasospastic.

Uses

1. Prophylaxis and treatment of angina. They are used in exertional angina and to relieve coronary spasm in Prinzemetal angina (rest angina).
2. Being smooth muscle relaxant, they find a place in the treatment of gastroesophageal spasms and nutcracker esophagus.
3. Intravenous nitrates can be used in unstable angina, acute myocardial infarction with or without left heart failure, to control blood pressure in preoperative hypertension and treatment of malignant hyperten-sion. They can be used for control of hypertension during surgery.
4. Being, venodilators they reduce portal venous pressure, may, sometimes be useful for treatment of acute variceal bleed due to portal hypertension.
5. Nitrates with calcium channel blockers can be used for treatment of angina with CHF, sick sinus syndrome and conduction disturbance.

Drug Dosage and Route of Administration (Table 3.7)

Potassium Channel Activator (Nicorandil)

Nicorandil belongs to a new class of antianginal agents called *potassium channel activators.* It causes venoarteriolar dilatation. It acts by increasing membrane conductance to K^+ ions which causes hyperpolarization of vascular smooth muscle membrane, thus reducing their excitability and leading to arteriolar dilatation. Unlike, nitrates, tolerance does not develop to nicorandil—an added advantage over nitrates. Being both venous and arteriolar dilator, it increases coronary blood flow and perfusion of poststenotic regions of the myocardium without causing a *"coronary steal-syndrome"* and restores the balance between O_2 supply

Table 3.7: Commonly used nitrates

Drug	Usual dose	Side effects	Contraindications
1. Sublingual nitroglycerine	0.3-0.6 mg	Headache, flushing, dizziness, tachycardia, hypotension	Intolerance or side effects
2. Isosorbide dinitrate (short-acting)	80-120 mg	Flushing, headache dizziness, tachycardia, GI upset and sleep disturbance, methemoglobinemia, cyanosis	As above. There may be worsening of ischemia on withdrawal
3. Transdermal nitroglycerine (skin patch)	0.4-1.2 mg/hr for 12-24 hr	Same as above	Same as above
4. Isosorbide-5 mononitrate (long-acting)	20-30 mg bid or 40 mg od	Same as above	Same as above

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