B. 13 Antihypertensive drugs

a. Classify the modes of action of the antihypertensive drugs.

central sympathetic tone inhibitors
  \( \alpha_2 \) agonists
  \( \beta \) antagonists
peripheral sympathetic antagonists
  \( \alpha \) blockers
  adrenergic neurone blockers (obsolete)
vasodilators
  arteriolar
    \( \text{Ca}^{2+} \) blockers
    others
  arteriolar and venous
    nitrates
ACE inhibitors
  ATII\(_1\) receptor antagonists
  diuretics

b. Describe the pharmacology of centrally acting agents such as clonidine and \( \alpha \)-methyldopa.

clonidine
  a selective \( \alpha_2 \) antagonist with central, spinal and peripheral actions
  available as oral, transdermal, IV, epidural and intrathecal preparations
  a weak base
  pharmacokinetics
    95% bioavailable, 20% protein bound, \( V_d \) 2 l/kg, \( t_\beta \) 8-12 h
    lipid soluble, diffuses readily into the CNS
    renally cleared 50% unchanged
  pharmacodynamics
    binds \( \alpha_2 \) receptors, imidazoline receptors
    presynaptic effect in periphery inhibits noradrenaline release
    central effect
      reduces sympathetic tone
      increases parasympathetic tone
      accentuates baroreceptor reflex
      sedative, depressant (blocked by tricyclics)
      rebound hypertension and anxiety on withdrawal
  dose 0.2-1.2 mg/d orally
\( \alpha \)-methyldopa
  false transmitter substrate with central \( \alpha_2 \) agonist effect
  administered orally
  pharmacokinetics
    metabolized on the same pathway as DOPA, yielding \( \alpha \)-methylnoradrenaline,
    an \( \alpha_2 \) agonist
    50% bioavailable, 15% protein bound, duration of effect ~24 h
  pharmacodynamics
    central effects similar to clonidine with less \( \downarrow \text{CO} \)
    antagonizes dopaminergic transmission
    extrapyramidal effects
    galactorrhoea
    hepatic necrosis
    Coomb's test positive in 20%
haemolytic anaemia 1%
other central $\alpha_2$ agonists, guanfacine and guanabenz are similar to clonidine

c. Describe the actions of ganglion blocking agents and the pharmacology of trimetaphan.

Ganglion blocking agents include tetroethylammonium, hexamethonium, mecyamine and trimetaphan. They are all selective nicotinic-N antagonists, blocking transmission at all autonomic ganglia, the adrenal medulla and sites in the CNS (though the quaternary ammonium compounds do not penetrate the CNS readily). They are all obsolete.

trimetaphan
competitive nicotinic antagonist acting predominantly at autonomic ganglia
administered IV
pharmacokinetics
rapid onset and brief action
IV infusion allows titration of blood pressure
pharmacodynamics
binds nicotinic receptors in autonomic ganglia
reduces sympathetic transmission
marked postural hypotension
impotence
sedation
reduces parasympathetic transmission
constipation
urinary retention
dry mouth
glaucoma, blurred vision

Antihypertensives 2.B.13.2 James Mitchell (December 24, 2003)
pharmacokinetics
poorly elucidated, duration of action is unrelated to plasma half-life
pharmacodynamics
interferes with uptake and storage of endogenous amines in vesicles
depletes noradrenaline, dopamine and serotonin (and adrenaline)
acts both peripherally and in the CNS
mostly central effect at low doses
reduced sympathetic tone
sedation, depression
extrapyramidal effects
diarrhoea
↑ gastric acid secretion
dose 0.25 mg to 1 mg as a single dose (obsolete)

e. Appraise the use of β-receptor blocking agents, α-receptor blocking agents and calcium antagonists in the treatment of hypertension.

β-blockers
anti hypertensive and antidysrhythmic drugs also used for glaucoma and sedation
classification
non-selective (propranolol), β₁ selective (metoprolol, atenolol, esmolol), α and β antagonist (labetalol)
membrane-stabilizing (propranolol, labetalol)
partial agonist (pindolol, alprenolol)
pharmacokinetics
oral, ophthalmic and IV preparations
bioavailability and binding vary from drug to drug
half-lives are mostly 3-6 h except esmolol which is short-acting and a few long-acting drugs (penbutolol, nadolol)
metabolism
responsible for variability in plasma levels in hepatic or renal disease
hepatic oxidation or conjugation
labetalol, metoprolol, propranolol, most others
renal excretion
atenolol, sotalol
hydrolysis
esmolol

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bioavailability</th>
<th>Protein Bound</th>
<th>t½/β</th>
<th>Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>atenolol</td>
<td>50%</td>
<td>&lt;5%</td>
<td>6-7 h</td>
<td>Renal excretion</td>
</tr>
<tr>
<td>propranolol</td>
<td>33%</td>
<td>90%</td>
<td>4-6 h</td>
<td>Hepatic oxidation</td>
</tr>
<tr>
<td>metoprol</td>
<td>50%</td>
<td>10%</td>
<td>3-4 h</td>
<td>Hepatic oxidation</td>
</tr>
<tr>
<td>esmolol</td>
<td>n/a</td>
<td>50%</td>
<td>9 min</td>
<td>Hydrolysis</td>
</tr>
</tbody>
</table>

pharmacodynamics
some have (class Ia) membrane stabilizing activity
competitive antagonists at β-adrenoceptors
can always be overcome with sufficient catecholamines
β₁ effects
↓ HR, contractility, renin secretion
β₂ effects
↑ airway tone, vasomotor tone
↓ insulin release
adverse effects
bronchospasm, asthma
cardiac failure, heart block
worsening of Raynaud’s phenomenon
impaired glucose tolerance and mask hypoglycaemia

indications
hypertension
  more effective in high renin setting
  acts both by ↓ renin release and ↓ CO
angina (and cardiac/major surgery)
  ↓ CO, myocardial oxygen demand
  ↑ duration of diastole, myocardial perfusion
AMI
  proven to reduce mortality
  acutely via anti-anginal effects
  also antidysrhythmic
arrhythmia
  slow atrial rate
  slow AV conduction
  glaucoma, hyperthyroidism
Calcium channel blockers
  vasodilating and antidysrhythmic drugs

verapamil
  type I Ca$^{2+}$ channel blocker: phenylalkylamine
  inhibits opening of both fast Na$^+$ channels and slow Ca$^{2+}$ channels
  oral and IV preparations
pharmacokinetics
  10-20% bioavailable
  90% protein bound (albumin and AAG)
  hepatic metabolism
  $t_1/2$ $\beta$ 5 h L isomer more rapidly metabolized
  slower clearance with prolonged use
pharmacodynamics
  L- (active) and D-isomers
  type Ia and IV antidysrhythmic effects at low dose
  negative inotrope at higher dose
  vasodilator
  both Ca$^{2+}$ channel and $\alpha$-antagonist effects
  weak bronchodilator
  sedative (↓ MAC)
indications
  AF, SVT: slows A-V nodal conduction
  hypertension
  improves diastolic compliance in hypertrophic cardiomyopathy
adverse actions
  complete heart block
  especially with $\beta$-blockers or halothane/enflurane
  myocardial depression
  constipation
  impaired glucose tolerance
  potentiate neuromuscular blockers and local anaesthetic effects
  causes hyperkalaemia when given with dantrolene
nifedipine
  dihydropyridine Ca$^{2+}$ channel blocker
  oral, slow release and IV preparations
pharmacokinetics
poor absorption sublingually
50% bioavailable (oral)
90% protein bound (albumin and AAG)
t')/β 2h (slow release oral preparations available)
hepatic metabolism

pharmacodynamics
potent peripheral and weak coronary vasodilator
direct negative inotrope
site of action is dependent on pharmacokinetics
nimodipine has more cerebral effect
reflex (baroreceptor-mediated) tachycardia, ↑ CO
↑ risk of ischaemia
minimal effect on conduction
indications
hypertension
Raynaud's phenomenon
adverse actions
vasodilation
headache, flushing, peripheral oedema
constipation
hypotension

nimodipine
dihydropyridine with cerebral vasodilating activity
↓ risk of vasospasm and ischaemia in SAH
↓ Ca\(^{2+}\) entry to neurones may reduce cell death
light sensitive
administered IV 0.4-2 mg/h

diltiazem
benzothiazepine Ca\(^{2+}\) channel blocker active at both cardiac and peripheral sites
oral preparations
pharmacokinetics
40% bioavailable
80% protein bound
hepatic metabolism
t')/β 4 h but complex kinetics result from enterohepatic circulation
pharmacodynamics
similar to other Ca\(^{2+}\) blockers but fairly selective for coronary vessels
improves subendocardial perfusion
some antidysrhythmic effect
indications
angina
hypertension

f. Describe the mechanism of action of vasodilators such as hydralazine, ACE inhibitors and diazoxide.

Direct vasodilators are potent in reducing blood pressure acutely, but have little effect on blood pressure when used long term. Reflex responses to arteriolar vasodilation include immediate increase in cardiac output and venous return and baroreceptor-mediated increase in sympathetic tone causing tachycardia, increased contractility and reduced venous pooling. Reduced renal perfusion pressure and sympathetic outflow results in increased renin, angiotensin II and aldosterone levels and consequent fluid retention. These effects result in a maintenance of blood pressure with increased intravascular volume and myocardial workload.
Hydralazine

a directly acting arteriolar vasodilator
oral and IV preparations

pharmacokinetics
25% bioavailability
bimodal metabolism by hepatic acetylation
t₁/₂β 2-4 h

pharmacodynamics
binds to vascular tissue, effect longer than t₁/₂β
direct vasodilator via NO synthesis

adverse actions
vasodilation
headache, flushing, palpitations
sympathetic tone
anorexia, sweating, nausea
sporadic
SLE-like syndrome, neuropathy, fever

clinical use
5 mg bolus, titrated to effect
onset over 20 minutes

Minoxidil
oral (and topical) preparations

pharmacokinetics
high bioavailability
low protein binding
prodrug: sulfate is the active metabolite (long t₁/₂β)
t₁/₂β 4 h

pharmacodynamics
sulfate binds to K⁺ channels in smooth muscle
increased K⁺ conductance
hyperpolarized membrane
direct arteriolar vasodilator

adverse effects
major reflex increase in sympathetic tone
pretreatment with propranolol required

Hair growth

Diazoxide

a thiazide without diuretic actions
IV preparation

pharmacokinetics
onset of action 5 min
high protein binding
metabolism uncharacterized
some excreted unchanged
t₁/₂β ~24 h (duration of effect 4-12 h)

pharmacodynamics and effects
as for minoxidil except without hirsuitism

ACE inhibitors

effective in high renin hypertension (as are β-blockers)

pharmacokinetics
most are prodrugs, deesterified in the liver

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bioavail. (%)</th>
<th>t₁/₂β (h)</th>
<th>Daily Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>40-70</td>
<td>3</td>
<td>15-75</td>
</tr>
<tr>
<td>Enalapril</td>
<td>11</td>
<td>10-20</td>
<td>15-75</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>12</td>
<td>10-80</td>
<td>15-75</td>
</tr>
</tbody>
</table>
all renally cleared except fosinopril

pharmacodynamics
antagonize peptidyl dipeptidase
normally converts AT I to AT II and metabolizes bradykinin
↓ AT II, ↑ bradykinin
↓ aldosterone, ↑ Na⁺ and water loss
vasodilation

adverse effects

cardiovascular
initial hypotension, intraoperative hypotension
potent effect on fetal blood pressure
renal
precipitate failure with or without renovascular hypertension
K⁺ retention
other
dry cough (bradykinin-mediated)
neutropenia
altered taste, allergies
diuretics
in B 17

g. Describe in detail the pharmacokinetics and pharmacodynamics of sodium nitroprusside and glyceryl trinitrate including their toxic side-effects.

glyceryl trinitrate
direct vasodilator described in 1879
explosive
\[ \text{O}_2\text{N}-\text{CH}_2-\text{CH(O-NO}_2\text{-CH}_2-\text{O-NO}_2 \]
pharmacokinetics
binds to PVC, reduces predictability of dose
prodrug metabolized by hepatic nitrate reductase, \( t_{1/2} \) 2 min
\[ \text{GTN} \rightarrow \text{glyceryl dinitrate} + \text{NO}_2^- \]
nitrite can release NO, but glyceryl di- and mono-nitrate are the main active drugs
NO is liberated from the nitrates by an unknown reaction which displays saturability, causing rapid tolerance
pharmacodynamics
NO diffuses into cells, ↑ cGMP to produce effects
smooth muscle: promotes dephosphorylation of myosin light chain
↓ phosphorylated myosin → relaxation
CVS: coronary vasodilation, ↑ endocardial perfusion
venodilation > arteriolar dilation, ↓ MAP, ↓ myocardial work
↓ platelet aggregation, ↑ MetHb
respiratory: pulmonary vasodilation, bronchodilation
GIT, uterine relaxation
clinical use
75-150 µg/min IV, up to 500 µg/min
adverse actions
hypotension, headache, tolerance, methaemoglobinaemia

nitroprusside
direct vasodilator
\[ \text{Fe}^2+\text{(CN)}_5\text{N'O} \bullet 2\text{Na}^- \]
light sensitive
pharmacokinetics
rapid metabolism in red cells releases NO and CN⁻
CN metabolized to thiocyanate and renally cleared ($t_{1/2}$ 4-7 days)
short $t_{1/2}$: offset of action within 10 min

pharmacodynamics
  vasodilator in all tissues
  more arteriolar dilation than GTN
  pulmonary vasodilation
  loss of coronary autoregulation: potential for steal

clinical use
  0.5 to 10 $\mu$g/kg/min (up to 2 $\mu$g/kg/min for sustained use)

adverse effects
  cyanide toxicity if inadequate metabolism or sulfur donors
  causes cellular hypoxia
  treated with thiosulfate ($\uparrow$ thiocyanate) or hydroxycobalamin
  thiocyanate accumulation
  neurological toxicity: weakness, disorientation, fits
  inhibits iodide uptake: hypothyroidism
  methaemoglobinemia, hypotension, headache, tolerance
  some patients are resistant or display unacceptable tachyphylaxis

h. Describe the pharmacological significance of nitric oxide, its mode of action and toxic effects.

Molecule of the Year 1992

pharmacokinetics
  synthesized by nitric oxide synthetase
  arginine + O$_2$ (+ NADPH, Ca$^{2+}$, calmodulin) $\rightarrow$ citrulline + NO
  subtypes of NO synthetase
  I  brain, platelets in cytosol. Ca$^{2+}$, calmodulin dependent
      $\uparrow$ by NMDA stimulation
      $\downarrow$ by IV induction agents
  II  macrophage. Prolonged production after induction and activation
      responds to $\gamma$-interferon, cytokines, endotoxin
  III vascular endothelium. Ca$^{2+}$, calmodulin dependent
      responds to shear, bradykinin, ACh, 5HT, hydralazine...
  can be administered in inspired gas at 0.1-40 ppm
  metabolism
  highly reactive, spontaneous degradation with O$_2$ to NO$_2$, NO$_3^-$ and NO$_2^-$
  strong oxidant: Hb $\rightarrow$ MetHb
  $t_{1/2}$β seconds

pharmacodynamics
  vascular smooth muscle
  activates guanylate cyclase, $\uparrow$ cGMP, $\uparrow$ protein kinase activity, $\downarrow$ Ca$^{2+}$, relaxation
  macrophages
  oxidizes bacterial respiratory enzymes $\rightarrow$ death
  neurones
  neurotransmitter via $\uparrow$ cGMP, excitatory
  role in peripheral and central analgesia, pain wind-up, memory
  neurotoxic in non-NO neurones

clinical use
  inhaled pulmonary vasodilator
  improved V/Q matching (distributed according to ventilation)
  used in ARDS, neonatal hypoxic pulmonary vasoconstriction
  administered in N$_2$ to minimize NO$_2$ exposure
  potential for specific NOS inhibitors in septic shock

adverse actions

Antihypertensives  2.B.13.8  James Mitchell (December 24, 2003)
methaemoglobinaemia
NO₂ causes pulmonary oedema

i. Describe the pharmacology of ketanserin

ketanserin
  vasodilator, antihypertensive
  not marketed in Australia
pharmacokinetics
  t₁/₂β 15 h
pharmacodynamics
  5HT₁c, 5HT₂ antagonist
  ↓ platelet aggregation
  vasodilation
  weak α₁ antagonist
clinical use
adverse effects
  CNS: headache, drowsiness
  CVS: ↑ QT interval, torsade de pointes