

DIGITALIS & RELATED CARDIAC GLYCOSIDES

Background

- in the following notes the term *digitalis* is used to describe the entire group of cardiac glycosides
- a large number of plants contain cardiac glycosides, and these have been used by natives as arrow and ordeal poisons
- *Squill* was known to the ancient Egyptians and the Romans used it as a diuretic, heart tonic, emetic and rat poison
- *Strophanthus* was introduced by Sir Thomas Fraser in 1890
- digitalis, or *foxglove*, was mentioned as early as 1250 in the writings of Welsh physicians and was not described botanically until 300 years later, by Fuschius who named it *Digitalis purpurea*
- in 1785 William Withering published "An Account of the Foxglove and Some of Its Medical Uses: with Practical Remarks on Dropsy and Other Diseases"
- John Ferrier (1799) was the first to ascribe the primary effect of digitalis to its action on the heart, relegating its diuretic action as secondary

Chemical Nature

- each glycoside represents a combination of an *aglycone*, or genin, with 1 to 4 molecules of sugar
- the pharmacological activity resides in the genin, however the attached sugars modify the water/lipid solubility and potency of the glycoside
- the *genins* are related to the bile acids, steroids, sex & adrenocortical hormones,
 - *cyclopentanoperhydrophenanthrene* nucleus,
to which is attached an unsaturated lactone ring at C₁₇
- other substitutions at varying positions on the ring affect the pharmacokinetics
- all naturally occurring genins possessing a C₁₄-OH
- increased potency is achieved by a C₃-OH and this is present on clinically used glycosides
- digoxin and digitoxin are the only commonly used glycosides and these consist of the corresponding genin, plus 3 molecules of *digitoxose*, joined in glycosidic linkage at the C₃ position

Pharmacodynamics

- digitalis is most frequently used to increase the adequacy of the circulation in patients with CCF and to slow the ventricular rate in patients with atrial fibrillation or flutter

NB: the main action of digitalis is its ability to increase *myocardial contractility*

- its positive inotropic action results in,
 - a. increased cardiac output
 - b. decreased heart size
 - c. decreased venous pressure
 - d. decreased circulating blood volume
 - e. diuresis and relief of oedema
- as digitalis frequently causes a dramatic reduction in the ventricular rate, it was originally believed this was the main effect
- subsequently shown to be beneficial *irrespective* of the HR, its predominant effects being on contractility
- in addition to the cardiac effects, digitalis has a direct action on,
 - a. vascular smooth muscle
 - b. neural tissue
- the later being responsible for *indirect* cardiac actions of the drug
- finally, changes to the circulation brought about by digitalis frequently result in *reflex* autonomic & hormonal changes which affect the CVS

Direct Cardiac Actions of Digitalis

NB: effects both myocardial contractility and electrical activity

■ Myocardial Contractility

- produces a positive inotropic effect in a *dose dependent* manner
- the effects are similar for atrial and ventricular muscle
- the effects are qualitatively the same for normal and failing myocardium
- in isolated myocardial fibres digitalis results in,
 - a. increased peak force
 - b. increased rate of development of force & decreased time to peak tension
- these effects are similar qualitatively at all points on the length tension curve
 - for any given end-diastolic fibre length, digitalis increases the generated tension
- the effect depends on the initial state of the myocardium, being greater in depressed myocardium
- effectively shifts the failing pressure-volume loop to the *left*
- very high concentrations produce a reduction in the resting fibre length and partial *contracture* with decreased function
- this effect is a toxic one, unrelated to the therapeutic actions
- there appear to be 2 components to the inotropic effect,
 1. *inhibition* of the membrane bound Na-K-ATP'ase
 2. an increase in the slow inward Ca^{++} flux (i_{sl}) in phase 2

NB: both → an increased *intracellular* Ca^{++}

- usual doses have no direct effect on the contractile proteins, or the interactions between them
- digitalis glycosides bind specifically to the Na^+/K^+ -ATP'ase, *inhibit* its enzymatic activity and impair the active transport of the two cations
- this results in a gradual increase in the *intracellular* Na^+ and a gradual but small decrease in K^+
- these changes are small at therapeutic concentrations of the drug
- the increase in Na^+ is judged to be the crucial event, as in cardiac fibres intracellular Ca^{++} is exchanged for extracellular Na^+ via an *antiport*, and this transport is decreased as the intracellular Na^+ rises
- the probable consequence is an increase in the Ca^{++} stored in the SR, with a greater amount available during each AP for contraction
- therefore, any of the following will *increase* myocardial contractility,
 1. ↑ extracellular Ca^{++}
 2. ↓ extracellular Na^+
 3. ↑ intracellular Na^+

NB: this explains the observation that the force of contraction is roughly proportional to the extracellular ratio $[Ca^{++}]/[Na^+]^2$

- the positive inotropic effect of a reduction of extracellular K^+ can also be explained by this mechanism, as this inhibits the activity of the pump
- in addition, this increase in $[Ca^{++}]$ results in an **increase** in the i_{sr} during phase 2, thus more Ca^{++} is available during each AP, triggering the release of more Ca^{++} from the SR

■ Electrical Activity Purkinje Fibres

- some of the therapeutic and most of the toxic effects of digitalis can be related to its electrophysiological actions
- the effects of digitalis on the transmembrane AP and resting potential (RP) are dependent upon both the **time** of exposure and the **concentration**
- the following sequence of changes is observed,
 - a. initially
 - i. at low frequencies → APD is increased
 - ii. at high frequencies → no change is seen
 - b. later
 - i. APD is **decreased** due to shortening of phase 2
 - ii. associated increase in the slope of phase 4 depolarization
 - iii. the resting membrane potential, or **maximal diastolic potential**, decreases
 - c. the less negative RMP further shortens APD
 - d. AP amplitude and phase 0 $\delta V/\delta t$ both **decrease**
 - e. finally, at toxic levels,
 - i. RMP is further reduced
 - ii. V_{max} is reduced
 - iii. conduction is reduced and fibres become inexcitable
- the effects on **phase 4** depend upon the extracellular $[K^+]$,
 1. at low values the slope is further increased with resultant increased **automaticity**
 2. at higher concentrations, $[K^+] \geq 4$ mmol/l, transient depolarizations, or delayed after-depolarizations appear
- as toxicity progresses the amplitude of these ADP's increases to threshold level
- thus digitalis can initiate extra impulses by 2 means,
 - a. enhancement of normal **phase 4 depolarization**
 - b. appearance of **delayed afterdepolarizations**

■ Electrical Activity Other Specialised Fibres

- digitalis exerts direct effects on both the **SA & AV nodes**, and on the specialized conducting fibres of the atria
- at clinical concentrations, digitalis has little direct effect on the SA node, most of these effects are due to **reflex changes**
- toxic concentrations can depolarise the SA node and depress impulse formation
- high concentrations also depress the AV node, but as for the SA node, most of the clinical effects are mediated through reflex autonomic changes
- the **direct effects** cause,
 1. ↓ conduction velocity
 2. ↑ effective refractory period (ERP)
 3. ultimately complete AV block

- the specialised atrial fibres respond similarly to Purkinje fibres, but importantly digitalis enhances **automaticity** and causes ADP's leading to **atrial arrhythmias**
- atrial and ventricular muscle respond similarly to Purkinje fibres, the **reduction** in the **APD** is not marked but probably accounts for the **decrease** in the Q-T interval seen on the ECG
- the transmembrane AP's show an increase slope in phase 2 and a decrease slope in phase 3
 - S-T and T wave ECG changes

- in high concentrations digitalis decreases the RMP, V_{\max} and $\delta V/\delta t$
- thus, high concentrations decrease conduction velocity and may render the myocardium inexcitable
- digitalis **does not** cause phase 4 depolarisation in atrial or ventricular muscle
- however may induce **afterdepolarisations**

NB: in general, increases in digoxin →
normal **fast responses** → **slow responses**,

- i. decrease V_{RMP}
- ii. decrease $\delta V/\delta t$
- iii. decrease v_c
- iv. decrease V_{max}

Indirect Actions of Digitalis

- many of the effects of digitalis on the mechanical and electrical activity of the heart in situ, result from modification of both autonomic neural activity and the sensitivity of the heart to vagal and sympathetic tone
- the decrease in sinus rate seen in the failing heart is due to a glycoside induced **increase** in efferent **vagal tone**, and an associated decrease in sympathetic tone
- the increase in vagal activity appears to be mediated at several sites,
 1. the baroreceptors are sensitised
 2. effects on the central vagal nuclei and nodose ganglion
 3. modification of transmission at autonomic ganglia
 4. increased sensitivity of the SA node to ACh
- these effects are in addition to direct effects on the heart and circulation which modify the input to autonomic reflex mechanisms
- changes in sympathetic activity are complex,
 1. high doses decrease the sensitivity of the SA & AV nodes to CA's
 2. digitalis may inhibit neuronal re-uptake of NA
 3. toxic concentrations may enhance sympathetic activity
- NB:** thus, **noradrenaline** plays an important role in digitalis induced arrhythmias and β -blockers attenuate, or prevent some induced disturbances of ventricular rhythm
- these effects are complicated in the failing heart by pre-existing alterations of autonomic activity
- in the **normal** subject, digitalis may have a negligible effect on the sinus rate, however, the increase in vagal tone is still present, as the maximal exercise induced HR is reduced
- in the **failing heart**, the negative chronotropic effect may be marked, however, in this circumstance, attenuation of compensatory sympathetic tone contributes to the effect
- atrial fibres, both specialised and nonspecialised, are quite sensitive to the effects of ACh
- therefore, the indirect effects of digitalis have **marked** effects on the electrical activity of the atrium, predominating over the direct effects at therapeutic concentrations
- liberated **ACh** results in,
 - a. an increase in the RMP (more negative)
 - b. a decrease in latent automaticity of specialised fibres = decreased phase 4 $\delta V/\delta t$
 - c. a marked **decrease** in the atrial APD and ERP
- NB:** thus the indirect effects tend to **oppose** the direct effects
- conduction velocity is dependent on many variables, but if hyperpolarisation is significant, then conduction is slowed
- NB:** at therapeutic levels the most significant **atrial** effects are **- APD & ERP**
→ the atria may respond at much **higher rates**

Cardiovascular Pharmacology

- toxic concentrations of ouabain cause ADP's in atrial muscle
- the atrial RMP may be significantly reduced in a number of disease states and under these conditions the hyperpolarisation caused by digitalis may improve AP's and conduction
- this is due to liberation of ACh, as the effect may be blocked by atropine
- similarly, if there is abnormally enhanced phase 4 depolarisation, digitalis will reduce automaticity

NB: therefore, the initial state of the myocardium is an important determinant of the effects of digitalis

- the **AV-node** is strongly influenced by the indirect actions of digitalis
- the increased vagal tone and decreased sensitivity to CA's markedly effect the generation of the nodal AP and conduction
- ACh causes hyperpolarisation in some fibres, but more importantly decreases the AP amplitude (V_{\max}) and $\delta V/\delta t$ in phase 0
- further, the recovery of excitability is delayed
- these effects slow conduction through the node, possibly to the point of complete block, and greatly prolong the **ERP**
- the most important result is a diminished rate at which impulses can be transmitted to the ventricles
- this effect is enhanced during AF, or at rapid rates, because through its indirect effects on the atria, digitalis usually **increases** the rate at which impulses enter the margin of the node
- those impulses entering the node which are not propagated leave the tissue refractory in their wake → **concealed conduction**
- repetitive concealed conduction increases the fraction of time during which the node is refractory

NB: therefore, direct and indirect effects tend to have the **same** effect on the AV node

- the **His-Purkinje system** is predominantly influenced by the SNS and shows little response to alterations in vagal tone
- thus, in contrast to the former, the indirect effects of digitalis are mediated by alterations in SNS tone, and these result in only minor changes in the electrical activity of the conducting fibres of the ventricles

Effects on Electrical Activity of the Human Heart *In Situ*

- surprisingly, most studies of the human atrium have shown only minimal changes in the ERP
- the ERP of the **AV node** is prolonged due to the **vagal effect**, the antiadrenergic effect and the direct effects
- the refractoriness of the His-Purkinje system has only been studied by **retrograde activation**, because the refractoriness of the AV node usually prevents propagation of premature supraventricular impulses
- using this method, intravenous ouabain does not cause any significant change in conduction or refractoriness of His-Purkinje fibres
- in contrast, the functional and effective RMP's of ventricular muscle are slightly, but significantly decreased
- this may increase the interval during which ventricular premature depolarisations may induce reentry excitation through the specialised conducting system

- in **atrial fibrillation**, the principal action of digitalis in reducing the ventricular rate is its action on the AV node, leading to **concealed conduction** and an increase in the fraction of time during which the node is refractory
- this is especially prevalent in the failing heart, because vagal tone is usually low and sympathetic tone high under these circumstances
- the resulting rapid and irregular ventricular rate may significantly reduce cardiac output
- the minimal interval between ventricular responses is determined by the ERP of the AV node
- digitalis acts to reduce the ventricular rate by a second mechanism, through its effects on the atria, the increase in atrial frequency leads to a greater proportion of impulses reaching the node in a refractory state

- in **atrial flutter**, which normally occurs as a circus movement around some conduction obstacle, digitalis will convert the rhythm to **atrial fibrillation**
- this occurs as the indirect effects of digitalis are not equal on all portions of atrial muscle and the propagated wave front becomes **fractionated**, AF resulting
- however, the administration of atropine, by removing the indirect effects, results in slowing of the flutter frequency with eventual extinction of the propagated wave, due to prolongation of the ERP above the path length of the circus movement

- in **Wolff-Parkinson White** syndrome the effects of digitalis on the anomalous AV bypass tract are variable
- some reports have shown a decrease in the refractoriness of the anomalous tract, others have shown variable effects
- the main point is that digitalis **may decrease** the ERP of the **bypass tract** allowing the rapid atrial rate to be transmitted to the ventricles, with resulting VF
- this decrease in refractoriness is believed to occur in ~ **30%** of WPW patients, and thus digitalis is clearly contraindicated

■ ECG Effects

- even toxic doses of digitalis **do not** cause an increase in the duration of the QRS complex
- after a large oral dose effects may be observed within 2-4 hours, typically,
 - a. the T-wave becomes diminished, isoelectric, or inverted in one or more leads
 - b. the S-T segment may be depressed (when QRS is upward)
 - c. the Q-T interval is shortened (reverse "tick" T-waves)
 - d. later, the P-R interval may be prolonged, rarely > 0.25 sec
- the former may mimic ischaemia, and after exercise the J-point may also be depressed
- large doses occasionally change the size and shape of the P-wave
- in patients with WPW the QRS complex may be widened, probably by slowing conduction through the AV node without affecting the anomalous tract

NB: almost any pattern of ECG changes can be mimicked by digitalis, however, if the QRS widens during normal sinus rhythm, it is almost certainly the result of **concurrent disease**

Effects on the Cardiovascular System

- these are a composite of the effects on the heart, the reflex autonomic effects and effects on vascular smooth muscle
- the effects depend markedly on the initial state of the heart & circulation
- changes to the CO, HR, BP, EDV, and CVP depend also on whether the subject is,
 - a. at rest, or exercising
 - b. subjected to stress
 - c. receiving other agents, such as anaesthetic gases
- in the **normal heart** a rapidly acting agent, such as ouabain given IV, usually,
 - a. increases the systolic and mean arterial pressures reaching a maxima in ~ 5 mins
 - b. these then decline slowly over 30 mins
 - c. all of the indices of ventricular contractility increase, but not markedly
 - d. the HR decreases moderately
 - e. SV increases mildly and EDV is slightly reduced
 - f. the CO is stable, or falls slightly
- if the arterial baroreceptors are denervated the HR does not fall, indicating most of the slowing is due to **reflex activity**
- if the HR is maintained by pacing, the CO does not fall and the size of the heart often diminishes
- thus the ventricle is able to sustain, or increase SV against an increased aortic pressure, without an increase in end diastolic fibre length
- as the mean arterial pressure is increased without an increase in CO, the systemic vascular resistance must also increase

Cardiovascular Pharmacology

- this is due to direct **vasoconstriction** of arteriolar smooth muscle
 - digitalis also increases SNS outflow, however this is of minimal significance
 - its effect on vascular smooth muscle extends to the veins and this may be especially prominent in the hepatic veins with pooling of blood in the portal vessels
 - this is believed to be the mechanism of the reduction in CO seen after IV injection in normal subjects
 - in exercise, digitalis decreases the maximal running speed, maximal cardiac index and HR, however causes little change in the indices of LV contractility
 - if the decrease in maximal HR is blocked by concurrent administration of atropine, no significant changes are seen
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- in the **failing heart**, the predominant effect is the direct increase in contractility, however the reduction in sinus rate is also important
 1. the LV function curve is shifted to the left
 2. CO is increased - despite the decrease in HR
 3. LVEDV & EDP are reduced
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- with the improved tissue perfusion sympathetic tone is reduced, with a further reduction in systemic resistance, LV afterload, and improved renal perfusion
 - the increase in **renal perfusion** may involve some reflex action of digitalis on the myocardium
 - direct cardiac application in dogs results in an immediate decrease in sympathetic tone to the kidneys, efferent traffic probably in the vagus
 - digitalis constricts coronary arteries, however at therapeutic levels autoregulation predominates
 - if the heart is dilated and in failure, then digitalis will most likely improve the relationship between CBF and myocardial O₂ demand

Pharmacokinetics

■ Absorption

- absorption of digoxin after oral administration is somewhat variable and is dependent upon the type of preparation, ranging from 40-90%
 - differences do not arise from variation in the content of tablets from different manufacturers, but from differences in the rates of *dissolution*
 - absorption appears to be best with the hydroalcoholic vehicle
 - absorption can be retarded by,
 - a. the presence of food in the GIT
 - b. delayed gastric emptying
 - c. malabsorption syndromes
 - d. antibiotics, such as neomycin
 - e. steroid binding resins

 - in ~ 10% of patients, a substantial fraction of the ingested digoxin is converted to inactive metabolites, such as 2-hydroxydigoxin, by intestinal organisms
 - following absorption, peak plasma levels are typically reached in 2-3 hours, while the clinical effects peak at 4-6 hours
 - if a loading dose is not given, steady state plasma levels may not be reached until 1 week, since the plasma half life, $t_{1/2\beta} \sim 1.6$ days

 - absorption of digitoxin is much more complete, ranging from 90-100%, as the drug is more lipid soluble
 - no significant problems with bioavailability have been noted, but it is also influenced by factors (a-c) above
 - because of its extended half life, steady state levels are attained slowly and recovery from toxicity is protracted
- ** see G&G, table 30-1

■ Distribution

- the glycosides are distributed slowly in the body, in part due to their large volumes of distribution
- as for other drugs, the presence of CCF may slow the rate of distribution
- protein binding is,
 - a. digoxin ~ 25%
 - b. digitoxin ~ 95%
- the glycosides are distributed to most body tissues, with equilibrium myocardial concentrations ~ 15-30 times the plasma levels
- binding in skeletal muscle is about 1/2 that of the heart but this is the major tissue store
- tissue binding is decreased by a raised plasma K^+ levels and the V_{dss} may be altered in a number of disease states
- the time required for maximal effect of the glycosides is generally ~ 1 hr greater than the time to maximal tissue concentrations

■ Elimination

- **digoxin** is eliminated primarily by the **kidney**, being both filtered at the glomerulus and secreted by the tubules
- there is some reabsorption, and this may be significant when the rate of tubular flow is reduced
- a very few patients form the inactive metabolite dihydroxydigoxin, and therapeutic levels are almost impossible to attain in such individuals
- the elimination half life, $t_{1/2b}$ ~ **1.6 days**, is strongly dependent upon renal function and there is good correlation between the steady state levels for a given dose and the **creatinine clearance**
- interventions, such as the administration of vasodilators, may significantly alter elimination
- **digitoxin** is metabolised by the liver MFO system, one of the products being digoxin
- metabolism may be accelerated by hepatic enzyme inducing agents, including phenylbutazone, phenobarbitone, phenytoin, and rifampin
- the elimination half life, $t_{1/2b}$ ~ **7 days**, is not appreciably changed by hepatic disease due to the huge reserve for metabolism
- the drug does undergo enterohepatic recirculation, but only a small amount of the drug is eliminated unchanged through the intestines

Dosage & Administration

- digitalis is used almost exclusively for 2 purposes,
 1. to improve the circulation in CCF
 2. to reduce the ventricular rate in AF or flutter
- both of these require chronic therapy and it is necessary to establish and maintain adequate myocardial concentrations
- if digitalization is non-urgent, a maintenance dose may be given orally and the plasma levels assessed at appropriate intervals
- maximal effect will be seen at ~ 4 elimination half-lives
- if rapid digitalization is required a large loading dose is required due to the long half life
- this dose may be difficult to estimate, theoretically, $LD = D_{ss} \times V_{dss}$
- however, this must be adjusted for the condition of the individual patient and is based on prior estimates
- for **digoxin**, 1.0 mg may be given IV over 10-20 mins providing it is certain the patient has not previously received digitalis
- very often this is divided into two doses separated by 3-4 hrs
- the maintenance dose must be equal to the daily loss,
 - a. digoxin ~ 35% of the body store
 - b. digitoxin ~ 10% of the body store
- regardless of the size of the initial dose, after sufficient time ($> 4 \times t_{1/2\beta}$), the plasma level will be determined solely by the ***maintenance dose***
- this should be determined by observation of the patient, including the ECG, and estimation of the plasma levels

Digitalis Intoxication

- the toxic effects of digitalis are frequent and can be severe or lethal
- some studies have shown that up to 25% of hospitalised patients displayed some signs of toxicity
- **NB:** the single most frequent cause of intoxication is concurrent administration of ***diuretics*** that cause ***hypokalaemia***
- all available preparations of digitalis have narrow margins of safety and all can cause similarly severe toxic effects, the only difference is the duration of toxicity

■ Toxic Effects On The Heart

- there is little evidence that toxic concentrations have any deleterious effect on the mechanical activity of the heart
- such concentrations typically cause abnormalities of cardiac **rhythm** and AV **conduction**
- usually, abnormalities of the intraventricular conducting system are not seen and the QRS complex is not prolonged
- the concentrations measured in plasma provide only crude, but useful, guidance as to the likelihood of tissue toxicity
- disturbances of rhythm may also be caused by low tissue levels, be drug-induced, or result from other toxicity
- the drug is used principally in abnormal hearts and these are significantly more likely to suffer from rhythm disturbances, particularly if there is progression of disease
- the demonstration that **digitalis toxicity** is in fact the origin of the disturbance lies in,
 1. evaluation of the ECG
 2. estimation of the plasma drug level
 3. documented reversal of the effect on withdrawal of the drug
- although digitalis can mimic almost any disturbance, certain patterns are more suggestive,
 - a. marked sinus bradycardia, or complete SA block
 - b. atrial arrhythmias
 - premature depolarisations
 - paroxysmal supraventricular tachycardias
 - non-paroxysmal supraventricular tachycardias
 - c. disturbances of AV nodal conduction, with complete AV block and accelerated escape rhythms
 - escape beats
 - non-paroxysmal AV junctional tachycardias
 - d. disturbances of ventricular rhythm
 - premature depolarisations → coupled beats
 - ventricular tachycardia or VF
- the premature depolarisations in ventricular muscle are not caused by increased automaticity, being due to either **reentry** or **delayed afterdepolarisations**
- persistent VT probably results from increased automaticity in His-Purkinje fibres
- the likelihood, and probably also the severity of the arrhythmia are directly related to the severity of the underlying cardiac disease
- children appear to tolerate higher concentrations of digitalis in both heart muscle and the plasma
- this appears to be related to real differences in the sensitivity of young specialised fibres to the toxic effects of digitalis

■ Other Toxic Effects

1. anorexia, nausea & vomiting
 - often the earliest signs of intoxication, though, individual variation is high
 - N&V are due to a direct action of digitalis on the CTZ
2. diarrhoea may be noted, as may abdominal discomfort, or pain
3. headache, malaise and drowsiness are common symptoms
4. neuralgic pain
 - similar to trigeminal neuralgia involving the third part
 - may be the earliest, most severe, or the sole symptom
5. "digitalis delerium"
 - may occur with confusion, disorientation, aphasia and mental clouding
 - convulsions rarely occur
6. visual disturbance
 - common, with blurring, white borders or halos
 - color vision may also be affected with *chromatopsia*, usually for yellow & green
7. gynaecomastia
 - has been reported and may related to some oestrogenic activity of the molecule

Treatment of Intoxication

- the following steps are recommended,
 - a. withhold further administration of digoxin
 - b. admit to an ICU & monitor the ECG
 - c. withhold diuretics or other agents which may lower the plasma potassium
 - d. if a severe arrhythmia is present further treatment with,
 - phenytoin
 - lignocaine
 - potassium salts
- the administration of K^+ salts reduces the binding of digitalis to cardiac muscle and directly antagonises certain of the toxic effects
- prior to such administration the plasma $[K^+]$ should be determined, as if the initial level is high, a further increase may intensify AV block and result in cardiac arrest
- *phenytoin* is effective in atrial & ventricular arrhythmias, whereas *lignocaine* only in the later
- the other anti-arrhythmic agents, such as quinidine, propranolol, or procainamide, are effective at times but are associated with a higher incidence of induction of new arrhythmias
- also, quinidine may increase the concentration of digitalis in plasma
- *atropine* may diminish sinus bradycardia, sinus arrest, and second or third degree AV block
- the use of *electrical countershock* in the presence of digitalis is hazardous and may result in severe ventricular arrhythmias
- if the dose is massive, as in attempted suicide, F_{ab} *fragments* of antibodies to the glycoside may be administered which have a high affinity and remove the glycoside from tissue binding sites

■ Drug Interactions

- **quinidine** results in an increase in the plasma levels of digoxin in over 90% of patients
- the rise is proportional to the dose, and may be as high as 4-fold, the average being ~ **2-fold**
- the effect may be due to displacement of digoxin from tissue binding sites
- a reduction in the V_{dss} has been reported
- further, renal clearance is reduced by 40-50% in most patients
- when administered concurrently, the cardiac effects, and the likelihood of toxicity are enhanced
- a similar interaction may occur with digitoxin, however this has not yet been documented
- plasma digoxin levels are also increased by,
 - a. quinine
 - b. verapamil
 - c. amiodarone

- interactions with the potassium wasting **diuretics** are the most frequent cause of toxicity
- administration of ***b*-agonists**, or succinylcholine increase the incidence of arrhythmias
- a number of drugs decrease the renal clearance of digoxin,
 - a. nifedipine
 - b. amiloride
 - c. triamterene

- similarly, a number of agents induce hepatic enzymatic degradation of digitoxin,
 - a. phenylbutazone
 - b. phenobarbital
 - c. rifampin
 - d. phenytoin

ANTI-ARRHYTHMIC AGENTS

Def'n: an arrhythmia is,

1. an abnormality of **rate**, **regularity**, or **site of origin** of the cardiac impulse, or
2. a disturbance in **conduction** that causes an alteration of the normal sequence of activation of the atria and ventricles

NB: these may arise from abnormal impulse **generation**, altered **conduction**, or **both**

Abnormalities of Impulse Generation

- these may be divided into,
 1. altered normal automaticity
 2. abnormal generation of impulses

■ Altered Normal Automaticity

- only a few sites frequently display normal automaticity,
 1. the SA node
 2. the distal AV node
 3. the His-Purkinje system
- other sites can also develop normal automaticity, including the specialised atrial fibres of the internodal tracts and the fibres near the coronary ostia
- in the sinus node the rate can be altered by autonomic activity, or intrinsic disease
- increased vagal tone increases g_K and outward K^+ currents
 - **hyperpolarising** the membrane and decreasing the rate of depolarisation
- increased SNS tone increases both i_f and i_{sI} , increasing the rate of phase 4 depolarisation
- the precise mechanism of the sick sinus syndrome is unknown
- augmented automaticity in the His-Purkinje system is a common event
- these fibres are highly susceptible to \uparrow SNS tone, the mechanism being similar to above (i_f & i_{sI})
- CA's have a similar enhancing effect, but also shift the voltage dependence for activation of i_f to more positive values → current begins to flow earlier in phase 3
- the role of altered vagal tone is unsettled, functional vagal innervation to the ventricles being questionable
- under certain conditions, with normal SA activity and AV conduction, it is possible for the H-P system to usurp the activity of the SA node
- in disease, such as the sick sinus syndrome, it is common for the activity of the H-P fibres to also be depressed, thus producing very low rates when the SA node fails to fire

■ **Abnormal Generation of Impulses**

- these are generally due to two mechanisms,
 1. **automaticity**, where depolarisation occurs at a very low (relatively positive) V_m
 2. **triggered activity**, generation of impulses by afterdepolarisations which reach threshold
- both of these can cause the formation of impulses in fibres which are ordinarily incapable of automatic function
- Purkinje, atrial and ventricular fibres can all show spontaneous activity when the resting V_m is reduced to ~ -60 mV or less
- the ionic mechanism for this is unknown
- **early afterdepolarisations** are secondary depolarisations occurring before repolarisation is complete
 - they occur relatively close to the plateau of phase 2 and frequently oscillate before stabilising at either a high or low V_m
 - early ADP's are promoted by,
 - a. a decreased background outward current i_{K1} K^+
 - b. an increased background inward current i_{bi} Na^+/Ca^{++}
 - c. an increased residual i_{Na} during phase 2
 - d. an increased magnitude or duration of i_{Sr} Ca^{++}
 - e. a decreased magnitude of i_{X1} K^+
- Purkinje fibres tend to have two stable resting V_m 's,
 1. -70 to -90 mV
 2. -30 to -50 mV
- **delayed afterdepolarisations** are secondary depolarisations occurring early in diastole, after full repolarisation
 - these are not self initiating, but dependent upon a prior AP
 - they are seen in certain cell types exposed to,
 - a. catecholamines
 - b. digitalis
 - c. perfusates with a low $[Na^+]_o$, or a high $[Ca^{++}]_o$

NB: *all* of which tend to raise the $[Ca^{++}]_{ICF}$
- these can reach threshold and give rise to a single premature depolarisation, which may in turn be followed by another delayed ADP, which may again reach threshold, and so on

NB: thus, delayed ADPs may give rise to coupled **extrasystoles**, or **runs** of tachyarrhythmias

Cardiovascular Pharmacology

- a number of factors increase the amplitude of delayed ADPs, thus increasing the likelihood of them attaining threshold,
 - a. increases in the basic driving rate
 - b. premature systoles
 - c. increased $[Ca]_o$
 - d. catecholamines
 - e. digitalis and some other drugs
- these can readily be produced in the H-P fibres but are less frequent other cell types
- tachyarrhythmias generated in this fashion are dependent upon an initiating beat and cannot arise *de novo* → **triggered activity**
- however, once initiated, this activity can be self-sustaining and frequently resembles reentrant activity
- both this and reentrant activity may be triggered by, or terminated by, a single premature stimulus

■ Abnormalities Of Impulse Conduction

- reentrant arrhythmias are self sustaining but **not** self initiating
- for reentry to occur there must be,
 1. an anatomical or functional barrier to conduction forming a **circuit**
 2. a **unidirectional block** to conduction
 3. a circuit **pathlength** greater than the **AP wavelength** = $v_c \times ERP$
- frequently the ERP is long, the v_c is fast, and the pathways available are reasonably short
- thus, for reentry to occur,
 1. normal conduction must be markedly slowed
 2. refractoriness must be markedly shortened
 3. or both
- both the SA and AV node are regions where conduction is normally very slow, and disease processes which further reduce conduction permit reentry
- conduction may be slowed by either alteration of the fast responses, or the generation of slow responses
- the v_c of **fast responses** is critically determined by the resting V_m , as this determines the $\delta V/\delta t$ of phase 0
- when the V_m is between -50 to -65 mV, abnormal fast responses are generated which propagate slowly enough to permit reentry
- at less than -50 mV slow responses may be generated, or the fast response may be conducted decrementally, that is the adequacy of the propagated impulse as a stimulus to resting tissue lessens progressively

Cardiovascular Pharmacology

- in the voltage range in which slow responses emerge, both i_{Na} and the pacemaker current are fully inactivated
- **slow responses** are due predominantly to i_{ST} , which is relatively small in magnitude and leads to small amplitude with a low phase 0 $\delta V/\delta t$
- the resulting v_C is so slow that reentry may occur over very short pathlengths

- clinically, reentry is usually the cause of paroxysmal SVT, and in the H-P system is thought to be one cause of coupled VPB's and VT
- however, these are extremely difficult to distinguish from triggered activity

Specific Abnormalities of Rhythm

■ *Sinus Bradycardia*

- usually benign
- treatment with atropine, or pacing is occasionally required if there is associated hypotension
- when occurring suddenly during surgery may be due to hypoxia or hypoventilation

■ *Sinus Tachycardia*

- HR in excess of 100 bpm and may be due to,
 - a. CCF
 - b. hypovolaemia
 - c. hypoxaemia
 - d. sepsis
 - e. thyrotoxicosis
 - f. anxiety
- treatment should be directed toward the underlying cause and the rate should not be lowered unless the underlying cause is known

■ *Atrial Ectopic Beats*

- existence of an atrial pacemaker outside the SA node
- isolated PAC's are benign and require no treatment
- the nodal rhythm which may occur with halothane is similarly benign
- chaotic atrial rhythms may be associated with hypoxia, especially in patients with COPD
- no specific therapy is required and digitalis may be detrimental

■ *Supraventricular Tachycardia*

- atrial rate suddenly increases to 150-250 bpm, with normal intraventricular conduction
- may occur paroxysmally in fit young adults, in whom it is a benign rhythm
- major consideration is the adequacy of the cardiac output
- treatment includes,
 1. carotid sinus massage
 2. other manoeuvres to increase vagal tone
 3. IV verapamil → 75-95% conversion to sinus rhythm
 4. DC countershock - hypotension, pulmonary oedema, ischaemia
- digitalis, and/or propranolol may also be used, however not with verapamil
- digitalis should be used with caution due to the possibility of WPW

■ Atrial Flutter

- the atrial rate is ~ 250-350 bpm
- there is usually some degree of AV conduction block, most often 2:1 or 4:1
- may be paroxysmal or sustained
- DC countershock is the treatment of choice when the circulation is compromised
- digitalis, propranolol, or verapamil may be used to slow the ventricular rate in less urgent cases

■ Atrial Fibrillation

- this is most commonly due to underlying heart disease,
 1. ischaemic heart disease
 2. thyrotoxicosis
 3. rheumatic heart disease
 4. alcoholic heart disease
- DC countershock is the treatment of choice when the circulation is compromised
- digitalis, propranolol, or verapamil may be used to slow the ventricular rate in less urgent cases
- NB:** agents with *vagolytic* properties, such as *quinidine*, dysopyramide & procainamide, should **not** be used prior to digitalisation, as they may increase AV conduction and increase the ventricular rate

■ Ventricular Arrhythmias

- isolated VEB's arising during surgery necessitate the search for an underlying cause, as these may precede VT or VF
- the proximity of the VEB to the preceding T-wave and its morphology are not a reliable indicators of malignancy
- in ventricular tachycardia the rate is usually 150-250 bpm and may be paroxysmal or sustained
- the treatment of choice, as for patients with ventricular fibrillation, is DC countershock
- when sinus rhythm is attained, treatment with lignocaine or similar should be commenced until the condition stabilises

Anaesthetic Considerations

- arrhythmias arising during surgery are usually benign, and may result from,
 - a. mechanical stimulation - eg. intubation
 - b. hypoxia
 - c. hypercapnia
 - d. anaesthetic drugs

- patients receiving antiarrhythmic agents prior to surgery vary according to the agent and the severity of the underlying disease
- the following agents may be continued parenterally, with appropriate adjustments for increased bioavailability,
 - a. digitalis
 - b. procainamide
 - c. phenytoin
 - d. propranolol

- the following should not be used parenterally due to the high risk of myocardial depression,
 - a. quinidine
 - b. disopyramide

- digitalis should usually be continued in patients with supraventricular arrhythmias
- patients with ventricular disturbances may be considered and assessed for treatment with lignocaine, however, others believe that treatment need only be instituted on an as required basis, providing acute ischaemia is avoided

- altered pharmacokinetics are important, changes in the CO, liver blood flow, clearance and V_{dSS} may all alter effectiveness and side-effects
- concomitant drug therapy is also important, most of the antiarrhythmics increase the NMJ blocking effects of dTC
- another example is the increase in the free concentration of propranolol after heparin administration

Cardiovascular Pharmacology

Classification of Antiarrhythmic Agents

¹ Vaughan Williams'		
Class	Electrophysiology	Examples
I. Na-Channel Blockers Ia. Ib. Ic.	 ↓ phase 0 ↓↓ conduction v ↑ repolarisation ↑ APD ↔, ↓ phase 0 ↓ conduction v ↓ repolarisation ↓ APD ↓↓↓↓ phase 0 ↓↓↓↓ conduction v ± repolarisation ↔ APD	 quinidine disopyramide procainamide lignocaine phenytoin tocainide, mexiletine flecanide ecainide, lorcaïnide
II. β-blockers		propranolol atenolol, esmolol
III. Prolong Repolarisation	↑↑ repolarisation	amiodarone bretylium, sotalol
IV. Calcium Entry Blockers		verapamil diltiazem
¹ effects on v _c rated 1↓ to 4↓ from: Goodman & Gillman		

- some drugs have multiple actions and could be listed in more than one class
- when given to patients with heart disease, the effects on the ANS, haemodynamics, myocardial MRO₂ & perfusion may also be important

LIGNOCAINE

Pharmacological Properties

- the agent of choice for the acute suppression of most ventricular arrhythmias
- plasma concentrations required for antiarrhythmic activity ~ **1.5 µg/ml**
- side effects generally begin to appear at levels ~ 5 µg/ml, these include,
 - a. feelings of dissociation
 - b. dysaesthesiae, often perioral
 - c. dysarthria
 - d. tremor
 - e. nonspecific mental disturbances
- higher concentrations produce more serious side effects, including,
 - a. decreased hearing
 - b. disorientation
 - c. muscle twitching
 - d. grand mal seizures
 - e. respiratory arrest
 - f. abnormalities of cardiac conduction, including asystole
- administer with caution to patients with AF or flutter, as it may **increase** the ventricular rate
- however, when conduction is via an **accessory pathway**, lignocaine is useful in slowing the ventricular rate
- lignocaine decreases myocardial contractility, especially in diseased hearts

■ Cardiac Electrophysiological Effects

- unlike quinidine or procainamide, most of its effects on the heart are by **direct action**
- **no** important interactions between lignocaine and the ANS have been described

■ Automaticity

- depression of the human SA node is distinctly **unusual**, but may occur in patients with pre-existing disease
- therapeutic levels decrease the slope of phase 4 depolarisation in His Purkinje fibres, due to a decrease in the pacemaker current (i_{K2} or i_p) and an increase in the time-independent outward current
- it may also decrease automaticity in depolarised, stretched Purkinje fibres and afterdepolarisations induced by digitalis

■ Excitability & Threshold

- increases the diastolic electrical current threshold in Purkinje fibres, by increasing g_K , **without** affecting the resting V_m or the threshold V_m

■ Responsiveness & Conduction

- the relationship between V_m and v_C is little altered by lignocaine in normal Purkinje fibres
- however, lignocaine prevents fast responses at low values of V_m , this is also explained by an increase in g_K ($i_{K1} \rightarrow$ phase 0-4 **repolarisation**)
- the effects of lignocaine on conduction are also dependent upon the $[K]_o$,
 - a. $[K]_o < 4.5$ mmol/l \rightarrow little or no effect
 - b. $[K]_o > 5.5$ mmol/l $\rightarrow v_C$ reduced at all values of V_m
- because of the large safety factor for conduction, lignocaine usually has no significant effects
- in ischaemic tissue, conduction velocity is usually considerably decreased
- in tissues depolarised by stretch or a low $[K]_o$, lignocaine usually increases the v_C

■ APD & Refractoriness

- results in almost no change in the APD of normal specialised atrial fibres
- substantially **decreases APD** in Purkinje fibres and ventricular muscle, due to blockade of the small i_{Na} which normally flows during the **plateau**
- the ERP is also shortened but not to the same degree as the APD, $\therefore \uparrow$'s **ERP:APD** ratio

■ Effects on Reentrant Arrhythmias

- lignocaine can abolish ventricular reentry, either by,
 - a. establishing two-way conduction blockade, eg. ischaemia
 - b. improving conduction, eg. stretch or low $[K]_o$
- lignocaine is much less effective than quinidine or procainamide in slowing the atrial rate in AF or flutter, or in converting these to sinus rhythm
- this is in keeping with its minimal effects on atrial tissue

■ Effects on the ECG

- in striking contrast to quinidine or procainamide, lignocaine causes little or no change in the ECG
- the Q-T interval may shorten, but the QRS does not widen
- there is usually no change in the refractory period of the AV node, but this may be shortened in some patients, who show an increased ventricular rate in AF
- also, particularly in patients with bundle branch disease, lignocaine may cause complete AV block within the H-P system

■ Autonomic Nervous System

NB: in contrast to quinidine, procainamide, bretylium, disopyramide and propranolol, lignocaine has no significant effects on the ANS

Pharmacokinetics

- although well absorbed after oral administration, lignocaine is subject to extensive first pass metabolism → **bioavailability** ~ 33%
- many patients experience nausea, vomiting, and abdominal pain after oral administration
- it is almost completely absorbed after IM administration
- its kinetics after IV administration follow a two compartment model
- the **distribution half-life**, $t_{1/2\alpha}$ ~ 8 mins, is rapid and the apparent V_{dss} ~ 1 L/kg, though, this may be substantially reduced in patients with heart failure or hypovolaemia
- the **elimination half-life**, $t_{1/2\beta}$ ~ 100 mins, and essentially no lignocaine is excreted unchanged in the urine
- protein binding ~ 70%, mainly to alpha-1-acid glycoprotein
- lignocaine undergoes N-dealkylation to **monoethylglycine-xylide** (MEGX), which in turn is either N-dealkylated to **glycine-xylide** (GX), or hydrolysed to **2,6-xylidine**
- 2,6-xylidine is further metabolised to 4-hydroxy-2,6-xylidine, which appears in the urine
- MEGX & GX are found in significant concentrations in the blood of patients receiving lignocaine, the former has anti-arrhythmic activity
- MEGX has a $t_{1/2}$ of 120 mins, and GX a $t_{1/2}$ of 10 hrs
- ~ 75% of the GX is excreted in the urine as a further metabolite, 4-hydroxy-2,6-dimethylaniline
- the clearance of lignocaine is highly dependent upon **hepatic blood flow** and is extremely sensitive to changes in this parameter

Dosage & Administration

- as the clearance of lignocaine is directly proportional to the liver blood flow, conditions of reduced blood flow will result in increases in the steady state plasma levels
- standard practice is to use a loading dose of ~ 100 mg, this achieves therapeutic plasma and tissue levels, however, is short lived due to rapid distribution (see W&W fig. 16.3)
- the best solution is to use a number of bolus doses, ~ 8 mins apart, followed by an appropriate continuous infusion
- each bolus should be given over several minutes
- the usual maintenance dose ~ 20-60 $\mu\text{g}/\text{kg}/\text{min}$
- however, as the elimination $t_{1/2}$ is around 2 hrs, steady state will not be achieved for 8-10 hrs

NB: loading doses **do not** alter the time required to reach steady state

■ Precautions & Contraindications

- steady state concentration (C_{SS}) is dependent only upon the maintenance dose and the plasma clearance,

$$C_{SS} = D_M / Cl$$

- the **loading dose** is determined by the required plasma level and the volume of distribution,

$$D_L = V_{dSS} \times C_{SS}$$

- in **heart failure**,

- $\downarrow V_{dSS} \rightarrow D_L \sim \text{halved}$
- $\downarrow Cl \propto \downarrow \text{liver blood flow} \rightarrow D_M \text{ should be reduced}$

- liver blood flow and clearance are also reduced in disease states of the liver
- since the **half life** follows the relationship,

$$t_{\frac{1}{2}} = \frac{0.693 \times V_{dSS}}{Cl}$$

- patients with liver disease tend to have the longest half lives and times to reach steady state
- in contrast, patients with CCF have approximately normal half lives as both V_{dSS} and clearance are reduced

NB: as lignocaine has negative inotropic action, excess levels may decrease liver blood flow, reducing clearance and further increasing plasma levels

Drug Interactions

- the negative inotropic action of lignocaine may be potentiated by,
 - a. disturbances of acid-base, or electrolyte balance
 - b. hypoxia
 - c. other myocardial depressant drugs
 - d. pre-existing myocardial disease
- propranolol is particularly dangerous as in addition to its depressant effects on the myocardium, it decreases liver blood flow and leads to increased levels of lignocaine
- other **basic drugs** can displace lignocaine from its binding sites on ***α -1-acid glycoprotein***
 - ***cimetidine*** increases the free drug levels in plasma
- lignocaine appears to potentiate the effects of succinylcholine, and the duration of blockade produced by dTC may be prolonged by 25%
- at therapeutic levels, lignocaine reduces the MAC's for halothane and nitrous oxide by 10-28%

■ Lignocaine Resistance

- failure of response to lignocaine is less likely to occur if the following guidelines are remembered,
 1. therapy should not be ceased due to failure, or transient response to a single bolus dose
 2. due to the long time to steady state, toxicity may develop many hours after the commencement of therapy ("ICU psychosis")
 3. an eventual subtherapeutic maintenance dose may only become apparent many hours after commencement of therapy, and may be easily misdiagnosed
 4. the common practice of "tapering" lignocaine is based on the misconception that the drug is rapidly eliminated, cessation should be absolute, with observation of the patient as the plasma levels decline
 5. certain disease states require major changes in the dosage regimen
 6. plasma levels within, and even above, the therapeutic range have been observed during local anaesthesia

QUINIDINE

- a member of the *cinchona alkaloids*
- quinidine is the *dextrostereoisomer* of quinine, and has all of the pharmacological actions of this agent, including,
 - a. antimalarial
 - b. antipyretic
 - c. oxytocic
- however, its actions on the myocardium are far more potent than quinine
- prepared and given its present name by Pasteur in 1853

Pharmacological Properties

■ Cardiac Electrophysiological Effects

NB: direct effects on most cell types of the heart,
and also has indirect effects through the ANS

■ Automaticity

- minimal direct effects on the firing rate of the SA node, however may indirectly increase the rate through *vagal blockade* or increased SNS activity
- it may cause severe depression of the SA node in patients with the sick sinus syndrome
- substantially decreases the phase 4 depolarisation of Purkinje fibres and shifts the threshold V_m toward 0 V
- the later is due to use dependent alteration of fast Na^+ -channels
- quinidine can suppress arrhythmias caused by enhanced automaticity in the H-P system
- however, this effect poses a problem in the treatment of arrhythmias in the presence of AV block
- therapeutic concentrations of quinidine have little effect on abnormal automaticity in H-P fibres or delayed ADP's
- however, quinidine may prevent *triggered activity* by preventing the premature stimulus that initiates the process

■ Excitability & Threshold

- quinidine *increases* the diastolic electrical current threshold in atrial and ventricular muscle, and in Purkinje fibres
- thus, it also increases the threshold for AF or VF

■ Responsiveness & Conduction

- quinidine decreases the amplitude, overshoot and $\delta V/\delta t$ in atrial, ventricular and Purkinje fibres
 - V_{\max} is reduced proportionately
- these effects are **dose dependent** and are not accompanied by an alteration of the resting V_m
- the rate of rise of premature responses is particularly depressed and the effects on $\delta V/\delta t$ are greater at less negative values for V_m

■ APD & Refractoriness

- causes small, but significant **increases** in the APD of normal atrial, ventricular and Purkinje fibres
- the ERP of all these cell types is increased **more** than would be expected from the changes in the APD

■ Effects on Reentrant Arrhythmias

- quinidine is an effective agent due to its effects on APD, ERP and conduction velocity
- in circuit loops in Purkinje fibres, quinidine frequently converts one-way conduction block into two-way block, thus abolishing the circuit
- its effectiveness in atrial flutter and fibrillation is more complex
- Méndez *et al.*, have emphasized the importance of the **wavelength**, ($\text{ERP} \times v_c$), in relation to the **pathlength** in the maintenance and termination of circus movements
- thus, agents which effect one but not the other, will be more effective in abolishing circus movements
- quinidine increases the ERP but decreases v_c , which of these effects predominating in its anti-flutter activity being uncertain
- AF being probably due to **random reentry** of numerous fractionated wavelets, is critically related to,
 1. the inhomogeneity of the ERP of the tissue, and
 2. the mean ERP of the tissue
- vagal stimulation and cholinomimetic agents tend to perpetuate such arrhythmias, as they decrease the mean ERP and increase the distribution
- quinidine, by virtue of its direct and indirect anti-vagal actions, increases the mean ERP and decreases the inhomogeneity
- thus, the action of quinidine in AF is not related to its ability to "snuff-out" the dominant circus movement, but its ability to reduce the maximum possible number of wavelets for a given mass of tissue

■ ECG Effects

- at therapeutic levels, it results in a small increase in the HR, and increases in the PR, QRS, and QT intervals
- electrophysiological studies indicate that quinidine,
 - a. increases the ERP of the atrium
 - b. decreases the A-H interval, representing nodal conduction
 - c. increases the H-V interval
- QRS widening begins at low levels of quinidine and is dose dependent

■ Autonomic Nervous System

- possesses both atropine-like and α -adrenergic blocking activity
- this results in vasodilation and, via the baroreceptors, increased SNS activity
- together, the decreased vagal activity and enhanced β -activity may result in increased HR and AV nodal conduction in some subjects

Pharmacokinetics

- quinidine sulphate is absorbed rapidly following oral administration with peak plasma levels in 60-90 mins
- absorption of quinidine gluconate is somewhat slower and less complete, peak plasma levels not being reached for 3-4 hrs
- excluding active metabolites, usual therapeutic levels are $\sim 1.5-2 \mu\text{g/ml}$, with toxic effects being seen above $5-8 \mu\text{g/ml}$
- it may be given IM but causes pain and a substantial rise in the plasma CPK
- protein binding $\sim 90\%$ to both *α_1 -acid glycoprotein* and albumin
- quinidine distributes rapidly to most tissues except the brain, with an apparent $V_{\text{ass}} = 2-3 \text{ l/kg}$
- it is largely metabolised by the liver then excreted by the kidney, with most metabolites being hydroxylated at only one site, either on the quinolone or quinuclidine rings
- minimal levels of dihydroxy metabolites are found and some of these are active
- the extent of hepatic metabolism is highly variable, and there is dispute about any increase in the plasma levels with CCF or renal insufficiency
- quinidine is both filtered at the glomerulus and secreted by the proximal tubules, with passive back-diffusion occurring in the distal nephron
- the mean elimination half life, $t_{1/2b} \sim 6 \text{ hrs}$ (R:4-19 hrs)
- as quinidine is a *weak base*, its excretion is increased by acidification of the urine
- if the urinary pH increases from 6-7 to 7-8, the renal clearance is decreased by up to 50%, with increases in the plasma level
- this situation rarely occurs clinically

Dosage & Administration

- oral dose is 200-300 mg, 3-4 times daily, with steady state levels being attained within 24 hrs
- parenteral administration is associated with significant **hypotension** and should be avoided
- postoperatively, the free fraction of quinidine decreases due to increased levels of α_1 -acid glycoprotein and protein binding
- like procainamide, quinidine can potentiate **NMJ blockade** in patients suffering myasthenia gravis
- CCF, renal disease and liver disease are not thought to require any specific alterations in therapy

■ Precautions & Contraindications

- about 1/3 of patients will have some immediate response which will necessitate cessation of therapy
- once this is overcome, few extracardiac adverse effects are encountered
- however, as quinidine has a narrow therapeutic range, excessive concentrations in any patient will result in adverse effects

■ Cardiotoxicity

- above concentrations of 2 $\mu\text{g/ml}$ the QRS is progressively widened, and the dosage should be decreased if the QRS duration increases by $\sim 50\%$
- at higher levels SA arrest, high grade AV block, ventricular tachyarrhythmias, or asystole may occur
- conduction is slowed tremendously in all parts of the heart
- polymorphic ventricular tachycardia caused by quinidine overdosage is potentially fatal
- the following agents are useful in the treatment of **ventricular tachyarrhythmias** caused by quinidine,
 - i. sodium lactate
 - ii. glucagon
 - iii. catecholamines
 - iv. magnesium sulphate
- quinidine and its hydroxy metabolites may be removed by dialysis
- quinidine syncope, or **sudden death** may occur in patients on quinidine
- this may be the result of excessive quinidine, or due to concomitant digitalis toxicity
- patients with pre-existing QT prolongation, or those who develop marked QT prolongation, are particularly prone to this event
- a **paroxysmal ventricular response** to AF may occur due to,
 - a. a reduction in concealed conduction, and/or
 - b. quinidine may be anticholinergic in some patients
- this is not common in patients treated only with quinidine, however, the response may be so dramatic that patients are frequently digitalised prior to therapy with quinidine

■ Blood Pressure

- may result in profound *hypotension*, particularly when given IV
- this is the result of vasodilation, with little change in CO
- very high levels may depress contractility

■ Arterial Embolism

- following conversion of AF to sinus rhythm, may occur from the LA appendage resulting in stroke, or other embolic phenomenon
- however, the risk of this is greater if fibrillation persists than if sinus rhythm is restored
- if cardioversion is performed as an elective procedure, it is usual to *anticoagulate* the individual 1-2 weeks prior to version

■ Cinchonism

- like other members of this class and aspirin, quinidine may result in tinnitus, vertigo, loss of hearing, blurred vision and GIT upset
- the skin may be hot & flushed
- abdominal pain, N, V & D are all likely to occur

■ GIT Disturbances

- these are the commonest side effects of quinidine therapy → N, V & D
- these may occur even at low plasma levels of the drug, and frequently occur early in therapy necessitating cessation of treatment

■ Hypersensitivity Reactions

- generally these are rare, but include,
 - a. fever
 - b. anaphylactic reactions
 - c. thrombocytopenia
- the later being due to drug-platelet induced Ab formation, with platelet aggregation and subsequent lysis

Drug Interactions

- agents which induce hepatic microsomal enzymes, such as phenobarbital or phenytoin, increase the clearance and reduce the half life
- when administered to patients with stable *digitalis* levels, the later frequently *increase* $\leq 2x$, due to a reduction in clearance and decreased tissue binding (V_{dss})
- occasionally, patients on oral anticoagulants will have an increase in the *OSPT* following administration of quinidine, the mechanism not being known
- as quinidine is an ***a-blocking agent*** it may interact with agents which cause vasodilation or decrease the blood volume, eg. nitroglycerin
- for any given [quinidine], the effects will be greater at higher $[K^+]$, ie. at lower values of V_m

Therapeutic Uses

- quinidine is a broad spectrum drug which is effective in the acute and chronic treatment of supraventricular and ventricular arrhythmias
- its principal use is chronic, to prevent occurrences of SVT, or to suppress ventricular arrhythmias
- individualization of the dose is usually required at the outset of therapy, due to the widely variable plasma levels and responsiveness of various conditions
- due to this, 24 hr Holter monitoring is frequently used to assess the effectiveness of therapy

PROCAINAMIDE

Pharmacological Properties

- the drug of choice for the acute treatment of lignocaine-resistant ventricular arrhythmias
- in general, its efficacy parallels that of quinidine, however some patients respond to one and not the other
- also has been useful in the treatment of some supraventricular arrhythmias, and has been used in the treatment of malignant hyperthermia
- therapeutic levels are usually $\sim 4 \mu\text{g/ml}$
- levels around $8\text{-}10 \mu\text{g/ml}$ produce side effects during chronic administration, possibly due to the production of NAPA

■ Cardiac Electrophysiological Effects

- the direct effects of procainamide on the myocardium are very similar to those of quinidine
- however, the indirect effects via the ANS are considerably different
- NAPA, (see below), accumulates in the plasma during chronic therapy and is less potent and qualitatively different in some actions to procaine
- chronic administration may result in widening of the QRS complex and prolongation of the Q-T segment

■ Autonomic Nervous System Effects

- the anti-ACh action of procainamide is much weaker than quinidine
- it does not produce α -adrenergic blockade, but may produce weak ganglionic blockade, thus impairing CVS reflexes

Pharmacokinetics

- procainamide is quickly and almost completely absorbed after oral administration
- peak plasma concentrations are reached at $45\text{-}75$ mins for capsules, and slightly longer for tablets ($W\&W = 0.5$ to 4 hrs)
- during the first week post-AMI, absorption may be reduced, peak plasma levels delayed and steady state levels sub-therapeutic
- SR formulations have a lower bioavailability and the absorption is delayed such that the duration of action may exceed 8 hrs
- plasma protein binding $\sim 20\%$
- rapidly distributed to most body tissues, excluding the brain, $V_{\text{dss}} \sim 2 \text{ L/kg}$
- however, the V_{dss} may be reduced to $\sim 1.5 \text{ L/kg}$ in patients with CCF or hypovolaemia
- metabolised in the liver to predominantly N-acetylprocainamide (NAPA)
- acetylation is subject to bimodal genetic variation, similar to isoniazid, dapsone, and other drugs
→ fast & slow acetylators
- in fast acetylators, or in patients with renal insufficiency, $\sim 40\%$ of the dose may be excreted as NAPA, and concentrations of NAPA in the serum may equal or exceed those of procainamide
- for optimal patient management, the plasma levels of both agents should be measured
- up to 60% of the dose is eliminated unchanged in the urine

Cardiovascular Pharmacology

- the usual elimination half life, $t_{1/2\beta}$ ~ 3-4 hrs
- procainamide is a weak base, and is filtered at the glomerulus, secreted by the proximal tubule and reabsorbed by the distal tubule
- moderate changes in the pH of the urine have only minimal effects on the excretion of procainamide
- however, when GFR decreases for any reason, serum levels of the drug significantly rise and the percentage metabolised in the liver increases
- the elimination of NAPA is virtually entirely by renal excretion and serum concentrations rise to dangerous levels in renal failure and CCF

Dosage & Administration

- available in tablets & capsules at 250 & 500 mg
- SR preparations from 250-750 mg
- solution = procainamide HCl, 100 or 500 mg/mL, suitable for IM or IV use
- the usual therapeutic range ~ 3-10 $\mu\text{g/ml}$
- the probability of toxicity increases markedly as the level rises above 8 $\mu\text{g/ml}$
- as for quinidine, the cardiac effects are enhanced if the plasma [K] is elevated, ie. the resting V_m is lowered
- the total loading dose ~ 7-10 mg/kg
- this should never be administered as a single IV injection as this will result in profound hypotension
- one rapid and safe method is intermittent intravenous administration, 100 mg is injected over 2-4 mins, at 5 min intervals until either,
 - a. the arrhythmia is controlled
 - b. adverse effects are seen
 - c. the total dose exceeds ~ 1000 mg, suggesting the arrhythmia under treatment is unresponsive
- this allows evaluation of the ECG and the BP between each dose, thus serious hypotension, or widening of the QRS can be avoided
- alternatively, a continuous infusion of ~ 275 $\mu\text{g/kg/min}$ over 25 mins
- the maintenance dose ~ 20-60 $\mu\text{g/kg/min}$ and as for any drug, steady state levels are not seen until 4-5 half lives (12-20 hrs)
- because of the narrow therapeutic range and the short elimination half life, oral dosing has to be at frequent intervals
- the usual starting dose is 250-500 mg every 4 hours
- monitoring of the plasma levels prior to the next dose allows assessment of the adequacy of therapy
- fortunately many of the patients have cardiac disease and the half life is prolonged, allowing q.i.d. administration
- oral loading doses are not recommended, as if the situation is urgent the IV route should be used
- the transition from IV to oral dosing requires ceasing of the infusion for approximately one elimination half life prior to the first dose, otherwise toxic serum levels may be reached
- procainamide may be used IM but this is rarely indicated

Precautions & Contraindications

■ Cardiotoxicity

- the incidence of adverse effects is high, and the effects are similar to those seen with quinidine
- the same rules apply for discontinuation of both agents
- high plasma levels produce VEB's, VT, or VF
- the syndrome of prolonged Q-T and marked ventricular arrhythmias is less frequent than with quinidine
- like quinidine, procainamide will slow the atrial rate in AF, and may thereby paradoxically increase the ventricular rate

■ Blood Pressure

- IV administration may result in acute hypotension
- prolonged, high serum levels may decrease myocardial performance and thereby promote hypotension

■ Extracardiac Adverse Effects

- anorexia, N & V, and rarely diarrhoea may result during oral administration, but these are less common than with quinidine
- procainamide has less CNS effects than either procaine or lignocaine, however, mild CNS symptoms may be seen

■ Hypersensitivity Reactions

- these are the most common and the most troublesome
- occasionally fever occurs in the first few days of therapy and forces discontinuation of therapy
- agranulocytosis may occur within the first few weeks with resulting severe infections
- systemic lupus erythematosus-like syndrome may occur
- first described by Ladd (1962)
- arthralgia is the most common symptom, pericarditis, pleuropneumonic involvement, fever, and hepatomegaly are common signs
- the most serious effect is haemorrhagic pericardial effusion with tamponade
- this syndrome differs from normal SLE, in that,
 - a. there is no female predilection
 - b. the brain and kidney are spared
 - c. leukopenia, anaemia, thrombocytopenia & hyperglobulinaemia are rare
 - d. false positive serological tests for syphilis do not occur
- the drug induced syndrome is reversible when the drug is ceased
- around 60-70% of patients receiving the drug will develop ANF Ab's within 12 months, however this is not a reason for discontinuation
- only 20-30% of this group will develop the SLE-like syndrome

- it is not yet proven that slow acetylators are at a greater risk of developing the syndrome, c.f. hydralazine where this is the case
- the use of acecainide (NAPA) has only rarely been associated with the development of ANF's
- other reactions include,
 - a. angio-oedema
 - b. skin rashes
 - c. digital vasculitis
 - d. Raynaud's phenomenon

■ **Other Precautions & Contraindications**

- a. renal insufficiency
- b. hypovolaemia
- c. CCF
- d. unexpected high $[NAPA]_{pl} \sim 20 \mu\text{g/ml}$
- e. myasthenia gravis → worsening NMJ blockade

DISOPYRAMIDE

- has similar electrophysiological effects to quinidine and is generally used for the treatment of ventricular arrhythmias

Pharmacological Properties

■ Cardiac Electrophysiology

- generally disopyramide causes,
 - a. little change in the sinus rate or the PR interval
 - b. shortens SA node recovery time
 - c. increases atrial refractoriness
 - d. no change in AV nodal conduction or refractoriness
 - e. QRS duration rarely increases > 20%
 - f. minimal change in H-P conduction
 - g. increased ERP of the ventricle
 - h. a consistent but small increase in the QT interval
- like quinidine, it has been associated with an accelerated ventricular response in atrial fibrillation
- disopyramide has atropine-like activity which nullifies some of the direct actions of the drug
- the relative potency is ~ 10% of that of atropine
- it has neither α nor β -adrenergic activity
- however, has a direct depressant effect on the myocardium and causes peripheral arteriolar vasoconstriction → reduced LV ejection
- this effect is more marked than for quinidine, procainamide, phenytoin, or lignocaine
- after IV administration BP increases despite the fall in CO due the intense increase in TPR

Pharmacokinetics

- oral absorption is ~ 90% and first pass metabolism is slight
- peak plasma levels are reached within 1-2 hrs
- at normal therapeutic levels (3 $\mu\text{g/ml}$), protein binding ~ 30%
- the apparent $V_{\text{dSS}} \sim 0.6 \text{ l/kg}$
- the major route of elimination is by the kidney, approximately,
 - a. 50% of the dose is eliminated unchanged
 - b. 20% as the mono-N-dealkylated metabolite
 - c. 10% as unidentified metabolites
- the elimination half life, $t_{1/2\beta} \sim 5-7 \text{ hrs}$
- however this may be significantly prolonged in renal insufficiency, $\leq 20 \text{ hrs}$

Dosage & Administration

- loading doses, particularly IV boluses are associated with an excessively high incidence of side effects and are not recommended
- not available (Aust/USA) for IV administration
- available as 100 & 150 mg capsules
- usual dose = 400-800 mg/daily, given q.i.d
- should be used cautiously in renal or hepatic failure
- untoward effects include,
 - a. anticholinergic effects
 - b. N, V & D
 - c. adverse haemodynamic effects
- when administered concurrently with warfarin, the requirements for the latter may increase

BRETYLIUM

Pharmacological Properties

- this is the only available antiarrhythmic agent which is a *quaternary ammonium* compound, and this may explain its unique ability to terminate VF in animal models
- highly effective in the treatment of refractory ventricular arrhythmias in man
- however, is frequently associated with adverse effects which are extensions of its therapeutic actions (see below)
- despite this, the use of the agent is limited to the treatment of acute ventricular arrhythmias, chronic therapy being investigational only

■ Cardiac Electrophysiological Effects

- bretylium has little direct effect on the following parameters,
 - a. automaticity - most changes are 2° to liberation of CA's
 - b. excitability & threshold - except for the VF threshold
- this is increased, independent of the SNS
 - c. responsiveness & conduction - except at toxic levels
- it causes a marked prolongation of the AP duration in Purkinje fibres and ventricular muscle
- the distribution of this change is such that the normal disparity between the APD's of various regions is reduced
- this effect is also seen in AMI models, where the differences between infarcted and normal tissues are reduced (canine)
- these effects are not seen in atrial fibres
- there are two postulated mechanisms for its ability to terminate *reentrant arrhythmias*,
 - a. the increased ERP without an alteration in conduction
 - b. release of CA's
→ repolarisation and increased conductivity in abnormally depolarised tissues
- the effects on the ECG include,
 - a. decrease in the sinus rate
 - b. increases in the Q-T and P-R intervals
 - c. little alteration in the QRS duration

■ Autonomic Nervous System

- bretylium has no effect on vagal reflexes and does not alter the responsiveness of cardiac cholinergic receptors
- following administration bretylium,
 - a. is concentrated in post-ganglionic adrenergic neurons displacing NA
 - b. blocks the neuronal reuptake of NA
- thus, the initial administration is associated with **hypertension** and possible worsening of the arrhythmia
- this is followed by **orthostatic hypotension**, with a pronounced postural component which is maximal during exercise
- this occurs because bretylium blocks vasoconstriction on standing and the tachycardia during exercise
- this is accompanied by supersensitivity to exogenous CA's
- the relationship of this effect to its antiarrhythmic effect is unclear
- blockade of its uptake into the nerve terminals by TCA's prevents its adrenergic effects but has little effect on its antiarrhythmic activity
- even in high concentrations bretylium does not directly alter the contractility of the myocardium, however this may increase due to the increase in CA's

Pharmacokinetics

- oral absorption is poor, usually ~ 40%, as expected for a 4° amine
- eliminated almost entirely by renal elimination without significant metabolism → 70-80% of an IMI dose
- the average elimination half life, $t_{1/2\beta}$ ~ 9 hrs, however this may increase to 15-30 hours in renal insufficiency

Dosage & Administration

- presently only recommended for the treatment of life threatening ventricular arrhythmias which fail to respond to treatment with a "first line" agent, such as lignocaine or procainamide
- given as a **loading dose ~ 5-10 mg/kg** slow IV push
- maintenance infusion rates at 1-4 mg/kg/min
- available as bretylium tosylate 50 mg/ml, 10 ml ampoules
- the main side effects are,
 - a. hypotension
 - which may occur with small doses and is not an indication of excess therapy
 - b. nausea & vomiting
 - c. parotid pain may occur with chronic oral therapy
- concurrent administration of TCA's prevents neuronal uptake and the propensity to cause ANS side effects

AMIODARONE

- a class III antiarrhythmic agent effective orally & IV in the treatment of ventricular and atrial arrhythmias
- an analogue of *thyroid hormone*, each 200 mg tablet containing 75 mg of organic iodine

Pharmacological Effects

- effects observed after acute administration frequently differ from those following chronic oral administration
- prolongs the APD, and hence the ERP, of atrial, nodal and ventricular tissues
- this explains its broad spectrum of activity
- decreases automaticity in the SA node by reducing the slow phase 4 depolarisation
- the increase in the ERP of atrial fibres is responsible for its effectiveness in SVT's
- decreases the conduction velocity and increases the ERP of the AV node, both *anterograde* and *retrograde*, making it particularly useful for reentry phenomena
- increases the ERP of H-P and myocardial fibres, however has *no effect* on v_c , reducing or preventing micro-reentry

Pharmacokinetics

- oral absorption is incomplete and erratic, **bioavailability ~ 22-86%**
- the elimination half life is long, **$t_{1/2b}$ ~ 14-59 days**
- the activity of the principal metabolite, *desethylamiodarone*, is unknown and its elimination half life longer, $t_{1/2\beta}$ ~ 60-90 days
- protein binding is extremely high and most of the drug is eliminated in the bile via the GIT
- the apparent V_{dSS} ~ 6.3 l/kg, and the drug accumulates in adipose and highly perfused tissues
- the pharmacokinetics after IV administration differ markedly
- removal being relatively rapid, $t_{1/2}$ ~ 20 hrs, due to *redistribution*

Cardiovascular Pharmacology

Dosage & Administration

- amiodarone is indicated for severe tachyarrhythmias → WPW, SVT, nodal tachy, AF, VF not responsive to other R_x
- treatment should be commenced in hospital and the patient should be regularly monitored for evidence of systemic toxicity, including,

- N & V - rarely constipation
- abnormal LFT's
- abnormal TFT's*
 - ↓'s peripheral conversion T₄ → T₃
 - ↓'s conversion in the pituitary → ↑ TSH levels
- cardiovascular effects - usually minimal, major advantage cf. other agents
 - atypical VT - Torsade de pointes
 - bradycardia
 - rarely exacerbation of CCF
- photosensitive skin rashes
- corneal microdeposits
- pneumonitis & interstitial pulmonary fibrosis

NB: * both *hyper* & *hypothyroidism* may occur and the onset may be abrupt

- due to I load assessment of the PBI, or I-uptake may be misleading
- monitoring is essential for several months after the discontinuation of therapy
- oral therapy should be tapered, starting with,
 - 200 mg t.d.s. for the first week
 - 200 mg b.d. for the second week
 - maintenance → minimum effective dose, usually 100-200 mg/d
- the maintenance dose should be regularly reviewed, especially when this is above 200 mg per day
- the high initial doses are required because of the slow onset of action whilst the necessary tissue levels are achieved
- IV administration is used where rapid control of rhythm is required
- infusion as 600 mg / 100 ml D₅W,
 - D_L → 5 mg/kg over 1/24
 - D_M → 10 mg/kg/day
- RAH uses 900 mg / 250 ml D₅W,
 - D_L → 100 ml over 1 hour → 360 mg
 - D_M → 10 ml / hr for 2 bags → ~ 900 mg/d

■ Drug Interactions

- a. digoxin - potential severe bradycardia
- b. β -blockers - potential severe bradycardia
- c. Ca-antagonists - potential severe bradycardia
- d. disopyramide - long QT syndrome
- e. procainamide - serum levels are significantly increased
- f. quinidine - long QT syndrome & atypical VT
- g. mexiletine - long QT syndrome
- h. warfarin - inhibits metabolism

PHENYTOIN

- principally used as an *anticonvulsant*, noted to be effective in the treatment of ventricular dysrhythmias in experimental AMI in the dog
- subsequent studies confirmed its efficacy in man, particularly in arrhythmias induced by *digitalis*
- it is also indicated in arrhythmias refractory to lignocaine, or in the oral treatment of chronic ventricular disturbances

Pharmacological Effects

■ Cardiac Electrophysiological Effects

- the effects are similar but not identical to those of *lignocaine*
- typical effects include,
 - a. no effect on the normal SA node
 - b. reversal of digitalis induced SA block
 - c. decreases abnormal automaticity in Purkinje fibres (i_{K1})
 - d. abolishes triggered activity and digitalis induced delayed afterdepolarisations
- the increased g_K induced by phenytoin, like that of lignocaine, makes it difficult to obtain responses at low levels of V_m
- further it can repolarise cells that have depolarised due to decreased membrane conductance
- the effects on the APD and on reentry phenomena are identical to lignocaine, viz.
 1. lignocaine prevents fast responses at low values of V_m , this is also explained by an increase in g_K (i_{K1})
 2. the effects of lignocaine on responsiveness are dependent upon the $[K]_o$,
 - i. $[K]_o < 4.5$ mmol/l \rightarrow little or no effect
 - ii. $[K]_o > 5.5$ mmol/l \rightarrow v_C reduced at all values of V_m
 3. because of the large safety factor for conduction, phenytoin usually has no significant effects
 4. in ischaemic tissue, conduction velocity is usually considerably decreased
 5. in tissues depolarised by stretch or a low $[K]_o$, phenytoin usually increases the v_C
- also like lignocaine, phenytoin has little effect on the ECG
- there is little effect on the AV nodal conduction in normal individuals, however, the AV nodal and H-P ERP's shorten significantly in digitalised patients

■ Autonomic Nervous System

- the effects are complex and most are centrally mediated
- decreases the efferent cardiac SNS traffic in patients with digitalis toxicity
- it may also modulate vagal activity by a central mechanism
- it has no peripheral adrenergic or cholinergic activity

Pharmacokinetics

- GIT absorption is slow and somewhat erratic
- absorption after IM injection is also incomplete
- protein binding ~ 90%, principally to plasma albumin, though, this is reduced in patients with renal insufficiency
- elimination is primarily by hepatic metabolism → hydroxylation
- these metabolites have no anticonvulsant activity and it is assumed that they have no antidysrhythmic activity
- metabolism is slow and not significantly influenced by hepatic blood flow
- in some individuals the pathway is saturable within the therapeutic range, minor changes in dosage resulting in large changes in plasma levels
 - dose-dependent elimination kinetics
- the elimination half life is long, $t_{1/2\beta} \sim 16-24$ hrs

Dosage & Administration

- therapeutic levels are ~ 10 µg/ml (total) and toxicity is frequently seen at levels > 20 µg/ml
- the usual **loading dose** ~ **10-15 mg/kg**
- IV administration is preferred for acute treatment, however, in order to avoid excessive hypotension the dose must be given slowly (< 50 mg/min)
- the usual practice is to infuse in 100 mg boluses until either the arrhythmia is controlled, or adverse effects are encountered up to 1000 mg
- the patient should be BP and ECG monitored
- the IV solution **pH ~ 12** and may result in severe phlebitis
- it should be administered undiluted as crystal precipitation may occur
- IM administration is not recommended as the drug may crystallize and absorption is unpredictable
- in less urgent cases, treatment may be commenced with an oral loading dose,
 - a. 15 mg/kg on day 1
 - b. 7.5 mg/kg on the days 2 & 3
 - c. 4-6 mg/kg/day for maintenance

Cardiovascular Pharmacology

- although anticonvulsant therapy may be achieved with a once daily regime, less fluctuation of the plasma level may be obtained with an 8 hourly dosing interval, and this may be desirable for antidysrhythmic therapy
- monitoring of plasma levels is essential as phenytoin *does not* follow first order kinetics
- occasional "slow metabolisers" may require as little as 100 mg/day, while some patients will require up to 800 mg/day
- drug interactions are known to occur with,
 - a. barbiturates
 - b. chloramphenicol
 - c. disulphuram, isoniazid
 - d. sulphonamides
- phenytoin itself may accelerate hepatic metabolism of other drugs,
 - a. digitalis
 - b. quinidine
 - c. disopyramide
 - d. oral anticoagulants
- the most prominent adverse effects are referable to the CNS, including,
 - a. nystagmus, vertigo and ataxia
 - b. nausea & vomiting
- these usually indicate plasma levels in excess of 20 $\mu\text{g/ml}$, and if the arrhythmia has not responded further increases are unlikely to be beneficial

Cardiovascular Pharmacology

LIGNOCAINE ANALOGUES

TOCAINIDE & MEXILETINE

- both agents closely resemble lignocaine in the chemical structures, pharmacological actions and therapeutic indications
- in contrast to lignocaine, both are effective after oral administration
- the effects of tocainide on the electrophysiology of specialised cardiac fibres and on the ECG intervals are virtually identical to lignocaine
- it has not yet been established whether its effects on ischaemic or damaged myocardium are the same
- in contrast to lignocaine, tocainide prolongs the ERP of the *accessory pathway* in patients with WPW syndrome, however, its efficacy in this condition is not established
- in general, the effects of mexiletine also resemble lignocaine, however its ability to reduce the automaticity of H-P fibres is more like quinidine
 - threshold firing V_m is shifted to a more positive value
- further, in patients with impaired AV nodal or ventricular conduction, mexiletine is more apt to reduce conduction velocities in the affected regions than is lignocaine

Pharmacokinetics				
	Bioavailability	V_{dss} l/kg	Cl ml/min/kg	$t_{1/2\beta}$ hrs
Tocainide	90%	3	2.6	13.5
Mexiletine	87%	9.5	10.3	10.4

- peak plasma levels of tocainide are seen within 2 hrs of oral administration
- up to 50% is eliminated unchanged in the urine
- the elimination half life may be increased two fold in patients with renal or hepatic disease
- only 10% of orally administered mexiletine is found in the urine, the remainder being hepatically metabolised
- both have been used orally and IV for the treatment of arrhythmias after AMI
- responsiveness to lignocaine is a good predictor for tocainide
- chronic oral treatment of VEB's with either drug has met with variable success

OTHER LOCAL ANAESTHETIC AGENTS

- encainide, flecainide & lorcainide all possess a pattern of electrophysiological effects which differ considerably from lignocaine
- this group may prove particularly useful in suppressing VPB's and ventricular tachyarrhythmias
- they have a fairly selective depressant action on the fast Na-channel
- effectively decrease V_{max} and AP overshoot in atrial, nodal and ventricular tissues → decreased conduction velocity, especially in the H-P fibres
- there are relatively minor effects on repolarisation, APD and ERP in Purkinje fibres
- AV nodal conduction velocity and ERP are usually unchanged by encainide & lorcainide, however, ERP's of accessory pathways are often prolonged
- the QRS is widened by all three agents, and excessive widening is an indication of overdose

Pharmacokinetics				
	Bioavailability	V_{dss} l/kg	Cl ml/min/kg	$t_{1/2\beta}$ hrs
Encainide	*			4
Lorcainide	*	6.4	17.5	7.6
Flecainide				7-24

- while all three agents are absorbed well orally, only flecainide is not subject to extensive first pass hepatic metabolism
- * encainide and lorcainide exhibit dose dependent bioavailability, which can be > 80% during chronic administration of maintenance doses
- two hepatic metabolites of encainide accumulate in the plasma during chronic administration,
 - a. O-demethylated-encainide
 - b. 3-methoxy-encainide
- the former has appreciable anti-arrhythmic activity and may be responsible for the AV depressant properties of the drug
- lorcainide is principally metabolised by aromatic hydroxylation, however also has an N-dealkylated derivative which is active and accumulates during chronic therapy
- all three appear to be beneficial in the management of PVB's
- successful suppression of VT has been more variable
- encainide & lorcainide may also be effective in the R_x of WPW syndrome

b-ADRENERGIC BLOCKERS

PROPRANOLOL

Pharmacological Effects

- most of the anti-arrhythmic activity can be explained simply on the grounds of *selective* β -blockade
- α -adrenergic and vagal mechanisms are left intact
- two other actions are also important,
 - a. increases of the background outward current i_{K1}
 - b. decreases of i_{Na} at high concentrations \rightarrow "quinidine-like" effects

■ Automaticity

- adrenergic stimulation significantly increases phase 4 depolarisation and the spontaneous firing rate of the SA node
- in the resting state, propranolol has little effect in the absence of SNS tone, however markedly decreases the response to exercise or emotion
- there may be marked slowing in patients with pre-existing nodal disease
- propranolol will decrease SNS enhanced activity in the H-P system and totally abolish automatic activity when this is induced by CA's
- like lignocaine & phenytoin, propranolol increases the background outward current, further decreasing automaticity

■ Excitability & Threshold

- neither the electrical threshold, nor the VF threshold are consistently affected in the normal heart
- however, propranolol increases the threshold for VF after experimental AMI

■ Responsiveness & Conduction

- only excessively high concentrations affect responsiveness of H-P fibres
- low amplitude premature responses are effectively abolished, probably via i_{K1}
- effectively slows intramyocardial conduction in ischaemic tissue, however has no such effect on normal fibres

■ APD & ERP

- little direct effect on the APD of the SA node, atrial, or AV nodal
- ventricular muscle APD shortens slightly and there may be marked shortening in the H-P system
- the ERP of the H-P system is shortened

NB: propranolol, by its β effects, results in a marked increase in the ERP of the AV node and this is its principal action as an anti-arrhythmic

■ Effects On Reentry

- there are many mechanism possible for its effectiveness in reentry,
 - a. the increase in AV nodal ERP
 - b. abolition of slow responses dependent on CA's
 - c. repolarise tissues depolarised by a decrease in g_K
 - d. abolition of depressed fast responses in ischaemic tissue
- at higher concentrations propranolol exerts "quinidine-like" effects on phase-0 depolarisation and responsiveness

■ Effects on the ECG

- a. increases the PR interval
- b. slight shortening of the QT interval
- c. no effect on the QRS duration
- d. no effect on the H-V interval at normal doses

Pharmacokinetics

- well absorbed orally, however is subject to variable and extensive first pass hepatic metabolism
- as with lignocaine, extraction is dependent on hepatic blood flow and is significantly reduced when this is decreased
- this is especially important for patients with cardiac insufficiency, when propranolol may decrease its own elimination by its effects on CO

VERAPAMIL

- this is a derivative of *papaverine* and was first used as a *coronary vasodilator*
- produces Ca^{++} -channel blockade in cardiac and smooth muscle membranes
- substantially slows the rate of impulse formation in the SA node *in vitro*
- however, this is offset *in vivo* due to *reflex SNS activity* resulting from arteriolar vasodilation
- normally the rate slows ~ 10-15%
- the drug has no significant effects on intra-atrial conduction
- decreases the rate of *phase 4* depolarisation in H-P fibres, and can block delayed ADP's and triggered activity resulting from digitalis toxicity
- the most marked effect of verapamil is on the *AV node*, where it decreases the conduction velocity and increases the ERP
- this presumably results directly from Ca^{++} -channel blockade, however is not seen at usual therapeutic concentrations of other Ca^{++} -channel blockers, eg. nifedipine
- the effect is unaltered by pretreatment with atropine or adrenergic blocking agents
- very effective in abolishing reentry rhythms in the ventricles which are a result of slow responses
- verapamil also has the ability to protect ischaemic cells and can reduce the level of damage during brief periods of ischaemia
- verapamil has no significant β -adrenergic or cholinergic blocking action, however does have some α -blocking activity

■ ECG Effects

- a. slows the SA rate
- b. prolongs the PR interval
- c. slows the ventricular response to AF

Pharmacokinetics

- absorption is good, however there is extensive first pass metabolism, oral *bioavailability* ~ 20%
- the extent of metabolism decreases with chronic administration and bioavailability improves
- effects are seen within 1-2 hours, reaching a maximum in 5 hrs
- the elimination half life, $t_{1/2\beta}$ ~ 5 hrs, and this also increases after prolonged administration
- the elimination half life is also longer in,
 - i. the elderly
 - ii. children
 - iii. cirrhosis - may increase up to 4 fold*

NB: *doses should be reduced by 80% for IV and 50% for oral administration

- norverapamil is an active metabolite, plasma levels during chronic administration reaching approximately the same levels as the parent drug
- this possesses ~ 20% of the anti-arrhythmic activity of verapamil
- the half life of norverapamil, $t_{1/2\beta}$ ~ 8-13 hrs
- after IV administration peak effects are seen within 10-15 mins

Dosage & Administration

- in the acute phase of PSVT, 5-10 mg slowly IV over ~ 2 mins
- to gain rapid control over the ventricular rate in AF 10 mg may be given over 2-5 mins and repeated in 30 mins if required
- chronic prophylaxis against PSVT requires 80-120 mg q.i.d.
- this is the drug of choice in the management of WPW

■ Adverse Effects & Drug Interactions

- the principal adverse effects are CVS and GIT
- the drug should be given with great caution to patients with dysfunction of the SA node
- verapamil is contraindicated in patients with,
 - a. any preexisting degree of AV block
 - b. severe LV dysfunction, unless precipitate by a rapid rate
- unexpected bradycardia, LV failure, hypotension, or AV block may occur in elderly patients given the drug IV, therefore the rate of administration should be slower in this group
- the ventricular rate may increase in patients with WPW syndrome and AF, due to reflex increases in SNS tone
- the major GIT side effect is constipation, but N & V may also occur
- the major drug interactions include,
 - a. β -blockers - significant bradycardia, or AV block
 - b. digitalis - significant bradycardia, or AV block
- decrease in digoxin clearance, cf. quinidine
 - c. antihypertensives which depress the SA node, eg. methyldopa, reserpine

Cardiovascular Pharmacology

Summary of Pharmacokinetic Data				
	Bioavailability	V_{dss} l/kg	Cl ml/min/kg	$t_{1/2\beta}$ hrs
Lignocaine	35%	1.1	9.2	1.8
Quinidine (SO ₄)	80%	2.7	4.7	6.2
Procainamide	83%	1.9	2.7*	3
Disopyramide	83%	0.6	1.2	6
Bretylium	23%	5.9	10.2	8.9
Amiodarone	35%	66	1.9	25 days
Phenytoin	98%	0.64	7.5	6-24
Tocainide	90%	3	2.6	13.5
Mexiletine	87%	9.5	10.3	10.4
Encainide	*			4
Lorcainide	*	6.4	17.5	7.6
Flecainide				7-24

VASODILATOR DRUGS

■ Classification

1. direct acting vasodilators
 - i. Nitric Oxide
 - ii. Nitroprusside
 - iii. Nitroprusside-Trimethaphan Mixture
 - iv. Nitroglycerine & Organic Nitrates
 - v. Purines
 - vi. Hydralazine
 - vii. Minoxidil
 - viii. Diazoxide
2. angiotensin converting enzyme inhibitors
 - i. Captopril
 - ii. Enalapril
3. α -adrenergic blocking agents
 - i. Phenoxybenzamine
 - ii. Phentolamine
 - iii. Prazosin
 - iv. Trimazosin
 - v. Doxazosin
4. dual α & β -adrenergic blocking agents
 - i. Labetalol
5. ganglionic blocking agents
 - i. Guanethidine
 - ii. Trimethaphan
6. centrally acting α -agonists
 - i. Clonidine
 - ii. Methyldopa
7. potassium channel "openers"
 - i. Pinacidil

Nitroprusside

- potent direct acting vasodilator, causing relaxation of both arteries and veins
- it has no important action on non-vascular smooth muscle and does not act directly on the myocardium or autonomic ganglia
- the major immediate clinical effect is a decrease in the arterial blood pressure

■ Mechanism of Action

- both nitroprusside and the nitrates activate *guanylate cyclase* to increase intracellular **cGMP**
- this presumably acts by either inhibiting the slow inward flux of Ca^{++} , or by inhibiting subsequent protein phosphorylation thereby relaxing the muscle
- thus, acts as an "intracellular nitrate", upon reaching the smooth muscle cytosol liberates *nitric oxide* (NO), the active moiety for nitrates
- supported by the potentiation of the hypotensive effect by *aminophylline*, a phosphodiesterase inhibitor, allowing accumulation of cGMP

■ Pharmacological Actions

- by virtue of its nonspecific vascular smooth muscle relaxant properties, nitroprusside has dominant actions on,
 - a. the CVS
 - b. the kidney
 - c. cerebral haemodynamics
 - d. the pulmonary circulation

■ Cardiovascular Actions

- SNP dilates both resistance and capacitance vessels with **no** direct effect on the myocardium
- thus, SNP decreases both systemic TPR and venous return
- the induced hypotension activates the sympathoadrenal system, with resultant *tachycardia*, increased myocardial contractility and renin release
- the usual response is an **increase** in CO
- however, this may remain unchanged or decrease slightly depending on,
 - a. the initial HR
 - b. the rate of lowering of the BP
 - c. the volume status of the patient
 - d. the presence of anaesthetic agents → modification of baroreceptor activity
- generally cardiac function improves in patients with chronic IHD
- SNP also antagonises potassium and NA induced contraction of vascular smooth muscle
- produces direct vasodilation in the coronary circulation, with increased CBF
- baroreceptor sensitivity increases following SNP-induced hypotension

■ Renal Effects

- increases RBF and sodium excretion in the isolated kidney
- however, in the intact animal, the **reduced** perfusion pressure reduces PAH and inulin clearance, and increases **renin** release

■ Cerebrovascular Effects

- SNP increases CBF and cerebral volume by a direct effect on cerebral vessels
- these effects may be undesirable in the presence of raised ICP
- maximal increases in ICP occur with modest reductions (<30%) in mean arterial pressure
- further reductions in the MAP result in decreases in ICP
- the presence of hypocarbia & hyperoxia will negate the increase in ICP seen when the MAP is dropped with SNP over 5 mins

■ Pulmonary Circulation

- pulmonary arterial pressures and vascular resistance fall
- a moderate to marked decrease in the P_{aO_2} is observed, probably due to an increase in the V/Q scatter, resulting from direct vasodilation
- inhibition of **hypoxic pulmonary vasoconstriction** may also be important
- during hypotension a $F_{I O_2} > 0.4$, plus monitoring with $SpO_2 \pm$ AGA's is recommended

■ Dosage & Administration

- due to the rapid onset of action and the evanescent nature SNP should be administered as a continuous IV infusion by a calibrated pump, with continuous IABP monitoring
- due to the potential for CN⁻ toxicity, the dose should not exceed,

- | | | |
|----|-------------------------------------|---|
| a. | short term administration (1-3 hrs) | < 1.5 mg/kg
< 25 µg/kg/1 hr |
| b. | chronic infusion | < 0.5 mg/kg/hr*
< 8 µg/kg/min |
| | * infusion 50 mg/100 ml | → < 1.0 ml/kg/hr |

- the required dose is **reduced** in the presence of,

a.	volatile anaesthetics	- baroreceptor sensitivity
b.	propranolol	- baroreceptor sensitivity - decreased renin release
c.	captopril	- decreased angiotensin II
d.	clonidine	- baroreceptor sensitivity - decreased renin release
- whenever **tachyphylaxis**, or resistance to the effects develops, the infusion should be ceased and another means of lowering the BP employed
- sensitivity to SNP increases in the elderly

■ Rebound Hypertension

- may occur after the sudden cessation of SNP, especially in the absence of adjunctive agents
- increase myocardial work and MRO_2 unfavorably in patients with IHD
- **pulmonary oedema** may occur in patients with pre-existing CCF and SNP should be terminated slowly, or the patient pretreated with propranolol or captopril
- rebound hypertension is not observed after SNP + trimethaphan

■ Clinical Uses

1. controlled hypotension during surgery
2. management of hypertensive emergencies
3. heart failure
4. idiopathic lactic acidosis → improved microcirculation
5. ergot poisoning

Toxicity of Nitroprusside

■ Metabolism

- SNP is metabolised in 2 stages, one nonenzymatic & one enzymatic
- in the **nonenzymatic pathway** an electron is transferred from the Fe^{++} of HbO_2 forming **MetHb**
- the resulting SNP molecule is **unstable** and releases all **5 CN^- ions**,



- there is also a nonenzymatic reaction between SH groups and SNP, but this is too slow to be important in humans
- these CN^- ions have 4 fates,

1. 60-70% **enzymatically** converted → **thiocyanate**
 - catalyzed by **rhodanese** in the liver and kidneys
 - requires thiosulphate and B_{12} as cofactors
 - rate limiting factor is the availability of endogenous **thiosulphate**
2. combination with MetHb → **cyanmethaemoglobin**
3. combination with hydroxocobalamin → **cyanocobalamin**
4. combination with tissue **cytochrome oxidase** → **toxicity**

NB: **hypothermia**, as during CPB, will not inhibit the reaction between HbO_2 and SNP, but will delay the enzymatic conversion of CN^- to thiocyanate, therefore **enhances toxicity**

- the amount of cyanide produced by SNP is **dose dependent**

■ Cyanide Intoxication

- this has been implicated in fatal reactions during SNP induced hypotension
- there is a **linear** correlation between the total dose of SNP and the blood [CN⁻]
- the earliest manifestations of the tissue hypoxia caused by **cytochrome oxidase** inhibition are,
 - a. an increase in the mixed venous P_{O₂}
 - b. a metabolic acidosis - type II **lactic acidosis**
- the development of **tachyphylaxis** to the hypotensive effect, despite adequate infusions of SNP should be considered a warning sign (CN⁻ directly antagonises the vasodilatation of SNP)
- other causes for this include low thiosulphate levels, or increased reflex SNS activity
- additional thiosulphate may be beneficial in patients who display tachyphylaxis after "normal" initial doses
- since the majority of patients developing tachyphylaxis are children and young adults, exaggerated **SNS reflexes** are the most common cause

■ Thiocyanate Intoxication

- this may occur with prolonged administration, especially in patients with **renal insufficiency** or hyponatraemia
- this is manifest by acute psychosis, muscle weakness, and nausea
- prolonged elevation may lead to hypothyroidism, methaemoglobinaemia and platelet inhibition

■ Treatment of Cyanide Intoxication

- aimed at the formation of MetHb and detoxification of CN⁻
 1. **oxygen** should be administered
 2. sodium thiosulphate ~ 150 mg/kg over 15 mins
→ S²⁻ ions necessary for the formation of **thiocyanate**
 3. sodium nitrite ~ 5 mg/kg over 3-4 mins
- reduces HbO₂ to **MetHb**
- competes with cytochrome oxidase for CN⁻ ions
 4. hydroxocobalamin ~ 5-10 mg slowly IV → **cyanocobalamin**

Nitroprusside-Trimethaphan Mixture

- used as a 1:10 mixture of SNP (25 mg) and trimethaphan (250 mg), in a solution of 5% dextrose
- the dose requirements of SNP and the whole blood CN⁻ levels are significantly reduced
- the incidence of tachyphylaxis, or rebound hypertension are far less
- a "hyperdynamic" circulation, as observed with SNP is not observed
- however, CO & tissue perfusion may be reduced

Nitroglycerine and Organic Nitrates

■ History

- NG was first synthesized in 1846 by Sobrero and developed for sublingual use the following year
- in 1857 Brunton administered amyl nitrite for the relief of anginal pain
- in 1879 William Murrell concluded that NG mimicked the action of amyl nitrite, and established its use in the R_x and prophylaxis of angina

■ Chemistry

- these agents are polyol esters characterized by a C-O-N sequence,

- a. organic nitrates = **nitric acid** = -C-O-NO₂
- b. organic nitrites = **nitrous acid** = -C-O-NO

- whereas the nitro compounds, which are not vasodilators, possess C-N bonds
- thus, **glyceryl trinitrate** is not a nitro compound and is erroneously called nitroglycerine (NG)
- in the pure form, without an inert carrier such as lactose, NG is explosive

■ Mechanism of Action

- the nitrites, organic nitrates, nitroso-compounds and a variety of other nitrogen oxide containing compounds activate **guanylate cyclase** to increase intracellular cGMP
- upon reaching the smooth muscle cytosol, these agents undergo **sulphydryl reduction** liberating the free radical **nitric oxide** (NO), which then interacts with and activates guanylate cyclase
- this leads to the formation of a cGMP-dependent protein kinase
 - eventually leads to the dephosphorylation of the myosin light chain
- depletion of sulphydryl groups (R'-SH) leads to a decreased effect with time
- an additional possible mechanism of action is inhibition the slow inward flux of Ca⁺⁺
- this mechanism is supported by the potentiation of the hypotensive effect by **aminophylline**, a phosphodiesterase inhibitor, allowing accumulation of cGMP

NB: all of these agents which act via nitric oxide have been termed the **nitrovasodilators**

■ Pharmacological Effects

■ Normal Subjects

- NG and the organic nitrates relax venous smooth muscle in low doses and arterial smooth muscle in higher doses
- the predominant effect of low doses is **venodilation** with reduced RV & LVEDP
- systemic arterial BP shows a mild to moderate decrease and the HR may increase slightly
- PVR decreases, whereas SVR usually remains unchanged
- dilation of the arteries of the face and neck produces the characteristic flush
- higher doses result in a fall in the arterial pressure and CO, with a **reflex tachycardia**

■ Ischaemic Heart Disease

- nitrates relieve anginal pain principally by reducing myocardial MRO_2 , through their effects on the systemic vasculature cf. coronary vasodilatation
- they decrease both preload and afterload
- **does not** increase total coronary blood flow in patients with atherosclerosis
- rather it has a selective dilating effect on the large coronary vessels, without impairing autoregulation in the small vessels which account for >90 of the CVR
- the net effect is a preferential increase in blood flow to ischaemic subendocardial regions

■ Other Effects

- these agents act on almost **all smooth muscle** including bronchi, biliary system, GIT, ureter and uterus
- cerebral vasodilation may lead to an increase in ICP in patients with reduced cerebral compliance
- NG produces a dose dependent increase in the **bleeding time**, without alteration of platelet aggregation
- spinal cord blood flow is maintained to mean arterial pressures of 60 mmHg, below which there is a parallel reduction in SCBF

■ Pharmacokinetics

- the biotransformation of organic nitrates is the result of reductive hydrolysis in the liver, catalyzed by **glutathione-organic nitrate reductase**
- this converts the lipid soluble organic esters into more water soluble denitrated metabolites and inorganic nitrite
- the partially and fully denitrated compounds are considerably less potent vasodilators than the parent compounds
- the liver has an enormous capacity for this reaction and biotransformation is the principal determinant of the duration of action
- following SL nitroglycerine peak plasma levels are seen within 4 minutes and the elimination half life, $t_{1/2\beta} \sim 1-3$ mins
- dinitrated metabolites have $\sim 1/10^{\text{th}}$ the potency as vasodilators and an elimination $t_{1/2\beta} \sim 40$ mins
- following SL isosorbide dinitrate peak plasma levels are seen within 6 minutes and the elimination half life, $t_{1/2\beta} \sim 45$ mins
- the rate of enzymatic transformation being $1/6-10^{\text{th}}$ that of NG
- the primary initial mononitrate metabolites have longer half lives (4-5 hrs) and these are responsible, at least in part, for the therapeutic efficacy of isosorbide

■ Dosage & Administration

- sublingual administration of NG 0.3 mg has an onset of action of 1-2 mins and a duration of effect lasting up to 1 hour
- buccal or transmucosal NG has a similar onset and duration of action
- oral administration requires the use of doses sufficient to overcome *hepatic metabolism*
- these are slow in their onset of action, peak effects at 60-90 mins, and have a duration of 3-4 hrs
- 2% ointment applied to 2.5 to 5 cms of skin provides gradual absorption and prolonged prophylaxis
- the total dose is 5-30 mg, the effects appear within one hour, with a duration of 4-8 hours
- NG disks are available which operate on the same principal, lasting ~ 24 hrs
- IV NG is marketed as ampules of 50 mg / 10 mls
- the solution is *not compatible* with PVC tubing

■ Indications

- a. myocardial ischaemia
 - acute ischaemia
 - unstable angina, AMI
 - coronary vasospasm
- b. intraoperative myocardial ischaemia
 - improves myocardial O₂ balance
 - preferentially increases blood flow to ischaemic areas
 - decreases preload and afterload
- c. acute and chronic LVF
- d. induced hypotension
 - beware of hypovolaemia
 - increases ICP
 - maintains tissue perfusion
- e. acute hypertensive crises
- f. pulmonary hypertension

■ Adverse Effects

- headaches, dizziness, postural hypotension
- drug rashes occasionally develop
- rarely *methaemoglobinaemia* has been reported
- the later is treated with methylene blue, 1-2 mg/kg, slowly IV
- dependence may develop and acute withdrawal may lead to AMI or sudden death

Adenosine

- most of the *purine* agents have acute vasodilating properties in most vascular beds
- adenosine is an important *autocoid* and endogenous vasodilator in man
- acts directly on *adenosine receptors*, P₁-purine receptors
- these are subdivided depending upon whether they inhibit (A₁) or activate (A₂) adenylate cyclase
- these are distinct from P₂-purine receptors, which are activated by ATP and are *not* blocked by the *methylxanthines*, cf. P₁-receptors which are
- ECF adenosine increases when O₂ delivery of is reduced or when ATP utilisation is raised
- therefore postulated to be important in regional regulation of blood flow,
 - a. dilates cerebral and coronary vessels
 - b. slows the discharge rate of CNS neurones and cardiac pacemaker cells
 - c. with noradrenaline and angiotensin II causes afferent arteriolar constriction
→ ↓ GFR and tubular MRO₂
- receptors are linked via G-proteins, not only to *adenylate cyclase* but to other effector systems
- conductance through one type of K⁺-channel in atrial tissue is directly linked to A₁-receptors
- this involves direct interaction of a G-protein with the channel, cAMP synthesis is unaffected
- adenosine itself is preferred to ATP, as the phosphate load released by the later may result in arrhythmias due to chelation of Mg⁺⁺ & Ca⁺⁺
- the adenosine uptake inhibitor, *dipyridamole*, potentiates the hypotensive effect
- adenosine is metabolised to inosine & hypoxanthine
- the plasma elimination half life, t_{1/2p} ~ 10-20 secs

■ Pharmacological Actions

1. induced *hypotension*
 - rapid onset, stable and readily reversible
 - decreased SVR, with CO is reflexly increased
 - HR, ventricular filling pressures and whole body MRO₂ are unaffected
 - lack of CA release and activation of the renin-angiotensin system probably accounts for the stability of the hypotension, without tachyphylaxis or rebound
2. direct *negative inotropic effect*
 - also inhibits the release of NA from SNS nerve terminals
3. *coronary blood flow* increases
 - however this *may* result in unfavorable redistribution and steal in subjects with IHD
 - myocardial ischaemia has been observed during adenosine hypotension in humans
4. *termination of PSVT*
 - demonstrated safely and effectively in older children and adults
5. pulmonary vascular resistance decreases but not to the same extent as SVR
6. decreased GFR in the kidney

Hydrallazine

- a phthalazine derivative, causing direct relaxation of arteriolar smooth muscle, especially in the coronary, cerebral, splanchnic and renal vasculature
- its mechanism of action involves activation of *guanylate cyclase* with increased levels of cGMP
- some interference with Ca^{++} flux across the smooth muscle membrane may also be involved
- the effectiveness of this agent is largely limited due to the profound reflex sympathetic and renin-angiotensin activation
- therefore has often been used concurrently with a β blocker

■ Pharmacological Effects

- lowers systemic BP due to arteriolar dilatation and decreased SVR
- diastolic BP usually falls more than systolic
- HR, SV & CO are all increased in response to vasodilatation
- in addition to the reflex SNS effect, the increase in HR may be due to a direct effect of hydralazine on the heart and CNS
- as the effects are predominantly on arterioles, postural hypotension is less common

■ Pharmacokinetics

- the drug is almost completely absorbed after oral administration, however is extensively metabolised in the liver
- oral *bioavailability* is low owing to variable first pass metabolism,
 - a. slow acetylators → 50%
 - b. fast acetylators → 30%
- the incidence of excessive hypotension and other toxicities is higher in the slow acetylator group
- these individuals should not receive more than 200 mg of hydralazine daily
- acetylation phenotype has little effect upon the plasma levels after parenteral administration
- peak plasma levels are seen at 30-120 mins after ingestion and this correlates with the peak hypotensive activity
- protein binding ~ 85%, mainly to albumin
- the plasma elimination half life, $t_{1/2\beta}$ ~ 4 hrs
- however, the effective half life ~ 100 hrs due to extensive binding of the drug by arterioles
- hydralazine is also metabolised by ring hydroxylation and conjugation with glucuronic acid

■ Dosage & Administration

- the usual parenteral dose is 10-40 mg/d
- the initial dose in a hypertensive crisis is 2.5-10 mg slow IV
- the onset of action is extremely variable and the effects develop gradually over 15-20 mins
- the duration of effect is 2-4 hrs
- initial oral doses are 25 mg t.d.s., increasing up to 40 mg q.i.d.
- maximum doses in women are reduced to 50 mg/d to reduce the incidence of SLE
- the duration after oral administration is 6-8 hrs

■ Adverse Effects

- important side effects include,
 1. reflex tachycardia
 2. fluid retention
 3. myocardial ischaemia
 4. drug induced SLE syndrome
 5. enhanced defluorination of enflurane
 6. peripheral neuropathy

Minoxidil

- this agent is a potent vasodilator which acts predominantly on arterioles
- the mechanism of action is possibly the same as hydralazine, though, it may also act via activation of K-channels

NB: decreases SVR → decrease in systolic and diastolic BP
→ reflex tachycardia, increase SNS and renin-angiotensin

- renal function often improves in patients with severe hypertension, however may decrease in patients with parenchymal renal disease
- the magnitude of the decrease in BP is proportional to the initial BP, the effect in normotensive subjects being minimal

■ Pharmacokinetics

- rapidly and completely absorbed from the GIT (~ 90%)
- peak plasma levels are seen within 1 hr and the maximal antihypertensive effect is seen in 2-3 hrs
- the elimination half life, $t_{1/2\beta}$ ~ 3 hrs, though, the antihypertensive effect may persist for 1-3 days
- metabolised in the liver, principally by conjugation with glucuronide
- some of the metabolites have pharmacological activity, though this is low
- only ~ 12% is excreted unchanged in the urine and severe renal disease impairs excretion

■ Dose & Administration

- the initial oral dose is 5 mg/d, increasing to 40 mg/d, given in one or two divided doses
- although doses of up to 100 mg/d have been given there is minimal therapeutic advantage in exceeding 40 mg/d

■ Adverse Effects

- the most common are,
 - a. fluid retention
 - b. hypertrichosis - especially face and arms
 - c. pericardial effusion in renally impaired patients
- therefore, often given with in combined therapy with,
 - a. a potent diuretic → decreased PT Na^+ reabsorption
 - b. a β -blocker

Diazoxide

- closely related chemically to the **thiazide diuretics**
- however, has an **antidiuretic action** → Na⁺ and fluid retention
- predominantly decreases arteriolar resistance and has some effect on the post-capillary venule
- the hypotensive effect is counteracted by reflex SNS activity
 - increased LV ejection velocity, HR & CI
- unexpected hypotension and increased contractility may precipitate myocardial ischaemia
- the increased ejection velocity may have adverse effects on a dissecting aneurysm
- as with other arteriolar vasodilators, the hypotensive effect may be exaggerated in hypovolaemic patients and those receiving β-blockers
- renal blood flow and GFR are reduced
- cerebral blood flow is decreased
- extrapyramidal symptoms may appear with prolonged use of the drug

■ Pharmacokinetics

- the plasma half life, $t_{1/2\beta} \sim 20-60$ hrs
- protein binding $\sim 90\%$
- this is decreased in patients with renal disease, therefore increasing the free fraction
- there is **no correlation** between plasma levels and the hypotensive effect as the drug is tightly bound to the arterioles
- successive doses having cumulative effects
- urinary excretion of the unchanged drug $\sim 1/3$ of the administered dose
- the remainder is metabolised in the liver

■ Adverse Effects

- a. fluid retention
- b. **hyperglycaemia** - inhibition of insulin release
- c. myocardial or cerebral ischaemia from excessive hypotension
- d. uterine relaxation during labor

■ Dosage & Administration

- now rarely used orally, reserved for the management of acute hypertensive crises
- usual dose = 1-3 mg/kg slowly IV
- a response is seen within 1-3 mins and the effect should last 6-7 hrs
- incremental doses can be administered at 15 min intervals

α -Adrenergic Antagonists

** for notes on phenoxybenzamine & phentolamine refer to notes on Adrenergic Blocking Agents

Prazosin

- the first member of a class of peripheral selective α_1 -blockers derived from quinazoline
- vasodilator activity is due almost exclusively to competitive postsynaptic α_1 blockade
- decreases the PVR and mean arterial pressure, with little or no increase in HR
- its selectivity is high and the absence of activity at presynaptic α_2 receptors is probably responsible for the minimal increase in HR and PRA
- may also act by "resetting" the baroreceptors and diminishing the sensitivity of the reflex arc
- venodilation occurs and the hypotensive effect is greater in the upright position, this may be intense after the *first dose*
- at clinically effective doses, the normal responses to cold, exercise and carotid sinus pressure are unaltered

■ Pharmacokinetics

- oral absorption is good and the drug undergoes first pass hepatic metabolism
- there is a linear correlation between the dose and plasma steady state levels
- bioavailability ~ 60%
- protein binding ~ 90%, principally to α_1 -acid glycoprotein
- the apparent volume of distribution, $V_{dss} \sim 0.6$ l/kg
- the elimination half life, $t_{1/2\beta} \sim 2-3$ hrs
- however, the hypotensive effect of the drug *does not* correlate with the plasma level, lasting up to 10-12 hrs
- this may be due to tissue binding, or to an active metabolite
- only small amounts of the unaltered drug are found in the urine
- dealkylated metabolites are eliminated in the bile
- in CCF and renal failure the free fraction is increased, however the half life prolonged, therefore the dosage should be reduced

■ Dosage & Administration

- initial oral doses are 1-2 mg t.d.s., increasing to 10 mg b.d.
- **first dose effect**, ~ 60-90 mins after administration may result in profound hypotension \pm LOC
- this is more likely in volume depleted patients (diuretics, CCF)
- therefore, the first dose is frequently administered at bedtime
- less common side effects include,
 - i. palpitations, tachycardia
 - ii. headache
 - iii. weight gain, peripheral oedema
 - iv. dry mouth, diarrhoea, constipation
 - v. eosinophilia
 - vi. hypersensitivity
 - vii. priapism

Trimazosin

- chemically related to prazosin and has a similar pharmacological profile, though, it is less potent at α_1 receptors
- well absorbed orally and extensively metabolised by the liver
- usual doses are 25 to 300 mg two or three times daily

Labetalol

- exhibits both selective α_1 & β -blocking activity
- possesses two asymmetrical C-atoms, thus is a mixture of four stereoisomers
- β activity compared with propranolol ~ 1 : 1.5-4 (ie. less potent)
- α activity compared with phentolamine ~ 1 : 6-10
- inherent α : β activity ~ 1 : 4-8
- it may possess a small degree of ISA at β_1 receptors
- in vivo, the relative α : β activity of labetalol is,
 - a. oral \rightarrow 1:3
 - b. IV \rightarrow 1:7
- however, the α effects are prominent in anaesthetized man

■ Pharmacological Effects

- given IV reduces SVR and BP in the supine position without significant reductions in CO or HR
 - pulmonary arterial pressures are also reduced
 - capacitance vessels are relatively unaffected by labetalol
 - decreases the hypertensive response to exercise and stress
 - orally does not reduce cerebral blood flow, despite a significant drop in arterial pressure
 - PRA decreases during long term administration
 - urinary and plasma CA levels are usually not elevated
 - also blocks neuronal reuptake of NA, though, this effect varies from tissue to tissue
 - some studies show no significant affect on FEV₁ in asthmatic subjects, while other showed worsening bronchoconstriction
 - no decrease in GFR or RPF in hypertensive subjects
-
- after oral administration a hypotensive effect is seen with 2 hrs and is maximal by 3 hrs
 - the average duration is ~ 8 hrs
 - after IV administration of 1-2 mg/kg to hypertensive patients, a significant fall in arterial pressure is seen within 5 mins

■ Pharmacokinetics

- well absorbed after oral administration but subject to extensive first pass metabolism
- oral bioavailability ~ 25%
- no active metabolites, principally eliminated by glucuronidation then renal and biliary excretion
- the elimination half life, $t_{1/2\beta}$ ~ 6 hrs
- the bioavailability is increased by concomitant administration of cimetidine
- also increased by significant hepatic disease
- both bioavailability and the elimination half life are increased in the elderly
- minimal transfer of the drug to the foetus

■ Dosage & Administration

- clinical uses,
 - a. essential hypertension
 - b. hypertensive crises
 - c. phaeochromocytoma
 - d. hypertension in pregnancy
 - e. ischaemic heart disease
 - f. intraoperative hypertension
- usual oral doses 100 mg b.d., increasing every 7 days to 600-800 mg/d
- IV doses 2.5-5 mg, given incrementally until the desired response is obtained
- side effects,
 - a. abdominal distention, diarrhoea
 - b. tingling scalp
 - c. occasional bronchospasm
 - d. urinary retention in males
 - e. postural hypotension
 - f. increased ANF and antimitochondrial Ab's

Trimethaphan

- often used for the induction and maintenance of controlled hypotension during GA
- its hypotensive action is due to,
 - i. ganglionic blockade
 - ii. direct relaxation of vascular smooth muscle
 - iii. α -adrenergic blockade
- histamine release does not play an important role in the hypotensive effect
- ganglionic blockade is via direct competition with ACh for *nicotinic receptors*

■ Pharmacological Effects

- the decrease in BP is due to a decrease in SVR, HR, SV & CO are usually unaltered
- CO may decrease if RA pressure is sufficiently lowered, or if the patient is in the head-up position
- the HR will increase if the initial vagal tone is high
- as the agent is a quaternary ammonium compound it has limited access to the BBB
- increases ICP, but to a lesser degree than SNP for the same degree of hypotension
- the slow onset of action for trimethaphan may allow time for cerebral autoregulation
- PRA and CA levels are not significantly elevated
- hepatic and renal blood flows unchanged, coronary BF decreased
- most of the drug is eliminated unchanged in the urine
- some may be subject to hydrolysis by BuChE
- side effects,
 - i. mydriasis, dry mouth
 - ii. GIT atony
 - iii. urinary retention
 - iv. postural hypotension
- *mydriasis* may interfere with neurological assessment following intracranial procedures
- may prolong the duration of action of *succinylcholine* due to competition for BuChE
- used almost exclusively for the induction of controlled hypotension, either alone, or in conjunction with nitroprusside (250 mg/25 mg)
- usually given as a continuous infusion of a 0.1% solution at 3-4 mg/min
- recovery from hypotension takes 15-35 mins and there is no rebound effect
- tachyphylaxis may develop after several hours of infusion
- other uses of the drug include,
 - i. hypertensive crises
 - ii. BP control in acute aortic dissecting aneurysm
 - iii. autonomic hyperreflexia
- the later is seen in patients with high spinal cord lesions → massive SNS discharge

Potassium Channel "Openers" - Pinacidil

- causes smooth muscle relaxation and vasodilatation which cannot be attributed to,
 - a. a central action
 - b. calcium channel blockade
 - c. stimulation of adenosine
 - d. prostaglandin formation
 - e. EDRF

- demonstrated in 1986 to increase the duration of potassium channel opening
- adverse effects include,
 - a. headaches
 - b. peripheral oedema
 - c. hypertrichosis

ALPHA-2 AGONISTS

■ Receptor Physiology

- single polypeptide chain, crossing membrane ~ 7 times
- intramembranous portion similar to other adrenoreceptors, contains NA receptor site
- cytoplasmic portion linked to **guanine nucleotide**, G-proteins, activating **cGMP**
- at least 4 different subsets of G-protein, G_{1-2-3} & G_0
- possible mechanisms of action include,
 1. **all** result in inhibition of **adenylate cyclase**
→ ↓ cAMP & dependent protein kinases
 2. ↑ K^+ efflux → ↑ K-channel opening
 3. ↑ Ca^{++} influx

■ Pharmacology

- 3 main classes,
 1. phenylethylamines - α -methylnoradrenaline
 2. imidazolines - clonidine, dexmedetomidine
 3. oxaloazepines - azepexole
- clonidine is a **selective partial agonist** → $\alpha_2:\alpha_1 \sim 200:1$
- effects are dependent upon the background NA level, when high clonidine acts as an **antagonist**
- dexmedetomidine is a **selective full agonist** → $\alpha_2:\alpha_1 \sim 1600:1$
- specific **imidazoline receptors** also exist which result in,
 1. vagotonia
 2. inhibition of steroidogenesis
 3. some other effects originally ascribed to α_2 activity

■ Neuroendocrine Responses

1. inhibit sympathoadrenal outflow
2. decrease release of neurotransmitter at neuroeffector junction
3. inhibition of ACTH release
4. inhibition of insulin release - direct effect on Islets of Langerhans
- short-lived, not clinically significant

■ Cardiovascular

1. postjunctional α_2 & α_1 mediate **vasoconstriction**, independent of neural input
→ IV clonidine may cause a transient **rise** in BP
2. α_2 mediated release of EDRF, **nitric oxide**
 - ∴ difficult *in vivo* to demonstrate direct constrictive effect, especially coronary
3. decreased **SNS outflow**
 - inhibition of activity in the **locus coeruleus** → depressed pressor response
4. bradycardia ? mechanism uncertain
 - enhanced baroreceptor sensitivity to systolic pressure elevation
 - presynaptically mediated inhibition of NA release
 - vagomimetic effect from the nucleus tractus solitarius
 - high doses will prolong AV nodal conduction and ↑ PR interval
 - no direct effect, nor α_2 receptor has been demonstrated on mammalian myocytes
5. decreased cerebral blood flow during anaesthesia

■ Respiratory

- i. no synergistic depression with the opioids
- ii. studies showing both bronchoconstriction & bronchodilatation

■ Renal ® Diuresis

- i. inhibition of ADH release
- ii. blockade of ADH activity at the tubular level
- iii. increased GFR
- iv. inhibition of renin release
- v. increased release of ANP

■ Gastrointestinal

- i. antisialogogue
- ii. inhibition of vagally mediated gastric acid secretion
→ no significant change in pH in humans
- iii. decreased vagally mediated gastric and SI motility

■ Anaesthetic Effects

1. **sedation** - EEG increased stage I & II sleep
2. **hypnosis** - pertussis sensitive G-protein conductance increase
- locus coeruleus
3. **analgesia** - dorsal root neuron inhibition of **substance-P** release
- higher levels, less well defined
4. successful pain relief administered epidurally
 - use as a sole agent limited by bradycardia, hypotension and sedation
 - prolongation and decreased dose requirements for opioids
5. effective for deafferentation pain and other states **nonresponsive** to opioids
 - more effective in management of trigeminal neuralgia than NSAIDs/opioids
6. decreased doses of IV induction agents
 - premedication associated with a high incidence of hypotension / bradycardia
 - may require concomitant use with anticholinergics in up to 50%
7. decreased **MAC** of volatile agents
8. decreased dose requirements for **induced hypotension** ~ 33%
9. improved **haemodynamic stability** pre & post-bypass despite decreased opioid doses
 - decreased muscle rigidity with high dose opioids
 - lower plasma catecholamine levels & blunted responses to intubation/sternotomy
 - decreased blood loss
 - reduction in intraoperative ischaemic episodes
 - higher post-bypass cardiac outputs & lower SVR
 - decreased times to extubation
10. reduction in **intraocular pressure** / blunted response to intubation
11. **antisialogogue**
12. decreased postoperative and epidural associated shivering
13. **cerebroprotective** effects in animal models of global ischaemia
14. increases **VF threshold** during halothane anaesthesia
15. decreased CVS effects of opioid/cocaine **withdrawal syndromes** perioperatively

Clonidine

- first used as a nasal decongestant & found serendipitously to have hypotensive effects
- the generalised depression, with reduced CO, HR & BP, results from decreased spontaneous discharge from the *splanchnic* and *cardiac nerves*
- peripherally, clonidine inhibits adrenergic transmission due to presynaptic α_2 activation
- this is most marked at *low* stimulation frequencies

■ Pharmacological Effects

- oral administration → decreased HR & SV in supine patients
decreased TPR if the patient is standing
- long term studies usually show HR & CI decrease more than does TPR
- the *bradycardia* is rarely severe and significant arrhythmias are uncommon
- the hypotensive effects generally parallel the reductions in circulating NA levels
- there is poor correlation between hypotension and the PRA or aldosterone levels
- clonidine *does not* block reflex SNS activity upon standing
- coronary vascular resistance decreases, independent of the decrease in MRO_2
- renovascular resistance decreases without altering RBF or GFR
- the capacity of clonidine to decrease PRA is lost if the kidney is denervated
- however, in the normal individual, the reflex increases in PRA seen with standing remain intact
- the agent is effective in patients with CRF and those undergoing dialysis

■ Pharmacokinetics

- oral absorption is almost complete and bioavailability is high
- peak plasma levels are seen at 1-3 hrs
- the elimination half life, $t_{1/2b} \sim 9 \text{ hrs}$
- plasma levels correlate with the hypotensive effect up to 2.0 ng/ml
- higher levels produce no addition effect and may increase the BP
- maximally effective plasma concentrations are seen after doses of 0.3 mg
- thus, there is little therapeutic advantage in increasing the b.d. dosage above this level
- the drug is highly lipid soluble and easily penetrates the CNS
- the apparent volume of distribution, $V_{dss} \sim 2.1 \text{ l/kg}$
- approximately half of the administered dose is degraded in the liver, the remainder eliminated unchanged in the urine
- no active metabolites are formed
- in patients with renal insufficiency the half life is significantly prolonged and the dosage should be reduced

■ Dosage & Administration

- the usual oral dose ~ 0.2 to 0.8 mg/d, administered in two or more divided doses
- administration of unequal doses, with the larger at bedtime eliminates some of the untoward effects of the drug
- available as 150 µg for IV administration in the management of hypertensive crises (**NB transient *increase* in TPR & BP)
- frequently encountered *side effects* include,
 - a. xerostomia
 - b. sedation

- up to 10% of patients cannot continue use of the drug due to persistent dry mouth, sedation, dizziness, nausea, indigestion, or impotence
- *xerostomia* is frequently accompanied by dry eyes, dry nasal mucosa, parotid swelling and anorexia
- used as a sole agent, frequently →
 - a. fluid retention
 - b. weight gain
 - c. loss of the hypotensive effect

- these are readily reversible by *diuretic* administration
- less common *side effects* include,
 - i. angioneurotic oedema
 - ii. urticaria
 - iii. alopecia
 - iv. pruritis and dermatological toxicities
 - v. hyperglycaemia
 - vi. urinary retention
 - vii. gynaecomastia
 - viii. elevated CPK

- sudden withdrawal of the drug may result in a profound *rebound hypertensive crisis*, which may be life threatening
- this is frequently accompanied by mass SNS overactivity, with tachycardia, sweating, abdominal pain, nervousness etc.
- this is usually seen at 18-20 hours after the last dose and rebound hypertension may persist for 7-10 days following cessation of treatment

Methyldopa

- one of the oldest antihypertensive agents, chemically a derivative of phenylalanine
- originally synthesized as an inhibitor of l-aromatic-amino-acid decarboxylase but was found to have antihypertensive action
- early theories on its mechanism of action included inhibition of the above enzyme and action as a "false neurotransmitter"
- currently believed to act via conversion to ***α -methylnoradrenaline***, which acts as a selective α_2 -agonist in the CNS, and like clonidine leads to a decrease in SNS outflow
- this mechanism is supported by,
 - a. inhibition of action by phentolamine
 - b. inhibition by prevention of decarboxylation in the CNS
 - c. hypotension does not correlate with reduced NA in CNS

■ Pharmacological Effects

- reduces TRP and BP without any significant change in HR or CO
- the fall in BP is maximal at 4-6 hrs following oral administration
- reductions in BP are greatest in the upright position
- although postural hypotension may occur, it is generally less than for other peripheral vasodilators
- PRA decreases, but this is not a dominant effect and is not necessary for the hypotensive effect
- plasma NA levels are decreased in all patients
- this correlates with the hypotensive effect but not with changes in RBF, plasma or total blood volumes
- if used alone, fluid retention, weight gain and loss of its efficacy are common
- in older patients, methyldopa may decrease the CO & HR
- oddly, treatment for 12 weeks or more may significantly reduce LV hypertrophy, without any apparent relationship to the change in BP

■ Pharmacokinetics

- oral absorption is variable and incomplete
- average bioavailability ~ 25%
- peak plasma levels are seen in 2-3 hrs
- elimination of the drug is biphasic, irrespective of the route of administration
- renal excretion accounts for ~ 2/3 of the clearance
- slow elimination of unidentified metabolites of the drug occurs in renal insufficiency and the dosage should be reduced

■ Dosage & Administration

- usual initial dose is 250 mg b.d., increasing up to 2 g/d
- once daily administration at night eliminates many of the adverse effects
- the most commonly reported side effects are,
 - i. sedation
 - ii. postural hypotension
 - iii. dizziness
 - iv. dry mouth
 - v. headache

- more important but less common problems include,
 - i. haemolytic anaemia
 - ii. thrombocytopenia
 - iii. leukopenia
 - iv. hepatitis
 - v. SLE-like syndrome

- with prolonged therapy, 10-25% will become *direct Coomb's positive*
- *haemolytic anaemia* occurs in ~ 5% of this group
- patients may remain positive for months after cessation of the drug
- hepatitis usually develops within 2-3 months of commencement of therapy, however may develop as late as 3 years
- transient abnormal LFT's appear in ~ 3%

ACE INHIBITORS

Captopril

- inhibits the conversion of angiotensin I to angiotensin II, principally in the lung
- present evidence suggests that the concomitant inhibition of the breakdown of *bradykinin* does not play a significant role in the action of these agents

■ Pharmacological Effects

- decreases SVR by increased compliance of large arteries and arteriolar dilatation
- systolic, diastolic and mean arterial pressures are reduced in the presence of hypertension
- in normotensive individuals only a small decrease is observed
- the initial reduction in BP correlates well with the pretreatment *plasma renin activity* (PRA)
- with continued treatment the correlation weakens and may be lost entirely
- patients with low renin activity show a slower and smoother decrease in their BP
- CO and SV are usually unchanged, and the HR may increase slightly
- CVS reflexes are maintained
- renal blood flow is increased with ensuing natriuresis
- cerebral and coronary BF's are well maintained
- aldosterone secretion is decreased but potassium retention rarely occurs
- in patients with CCF, CO is increased and there is an increase in exercise tolerance
- pulmonary vascular pressures are reduced

■ Pharmacokinetics

- captopril is well absorbed orally with a bioavailability ~ 65%
- peak plasma levels are seen at 30-60 mins and absorption is delayed by food in the GIT
- the elimination half life, $t_{1/2\beta}$, ~ 2 hrs
- the major route of elimination is via the kidneys (95%), with over 50% of the oral dose being eliminated unchanged, and this correlates with the *creatinine clearance*
- thus, the elimination half life is prolonged in renal insufficiency

■ Dosage & Administration

- the usual adult dose is 25 mg t.d.s., but may be increased up to 300 mg/d
- therapy is usually commenced with 1/4-1/2 this amount due to the first dose effect, preferably commenced in hospital with BP monitoring
- diuretics or β blockers should be ceased prior to commencement of therapy
- the dose should be lower in the presence of CCF, hypovolaemia, or diuretic therapy

■ Precautions & Adverse Reactions

- severe hypotension may occur, especially following the first dose in hypovolaemic patients (diuretic therapy) or CCF
- renal insufficiency may be precipitated in patients with bilateral renal artery stenosis
- despite the reduction in aldosterone, significant retention of potassium rarely occurs
- other side effects include,
 - a. erythematous rashes
 - b. disturbances of taste
 - c. vertigo
 - d. headache
 - e. GIT disturbances
 - f. neutropenia - rare but serious
 - g. proteinuria ~ 1% of patients
? association with membranous GN

■ Therapeutic Uses

- a. mild to moderate hypertension, all forms
except primary hyperaldosteronism
 - b. malignant hypertension
 - c. renovascular hypertension
 - d. hypertensive crises of scleroderma
 - e. dialysis resistant hypertension
 - f. pretreatment for induced hypotension in surgery decreases SNP requirements and rebound hypertension
- these agents are useful in diabetic and asthmatic patients, in whom they present no significant problem

Enalapril

- resembles captopril in its pharmacological and therapeutic actions
- is more potent and has a longer duration of action, probably due to increased enzyme binding
- this allows the drug to be used once daily
- unlike captopril, enalapril is **not a sulphydryl compound**, thus is devoid of many of the side effects of captopril
- rapidly absorbed after oral administration and is relatively unaffected by the presence of food
- unlike captopril, it is a **prodrug** and must be hydrolyzed in plasma to the active dicarboxylic acid, **enalaprilate**
- plasma levels of the later take 3-4 hrs to reach maximum, and the therapeutic effect lags behind this
- in contrast, IV administration of the parent acid results in significant effect within 15 mins
- daily doses range from 10-40 mg
- Enaprilat injection is available (not in Australia) as 2.5 mg in 2 ml vials