B. 14 Antidysrhythmic drugs

a. Classify antidysrhythmics by their electrophysiological actions.

Vaughan-Williams classification

I  membrane stabilizers
   all ↑ ERP, ↑ ERP/APD, all except c ↑ APD
classified by rate of dissociation
   a  medium
      ↑ QT, QRS
      quinidine, procainamide, disopyramide
   b  fast
      ↓ QT
      lignocaine, mexiletine, tocainide
   c  slow
      ↑ PR, QT, QRS
      flecainide, encainide, others

II  β-blockers
    in Antihypertensives (2.B.13)
    ↓ HR, ↑ PR

III  drugs prolonging repolarization
    ↑ APD, ↑ ERP
    ↑ QT, ↓ HR
    amiodarone, sotalol, bretylium

IV  Ca^{2+} channel blockers
    in Antihypertensives (2.B.13)
    ↓ HR, ↑ PR

others
   adenosine, digoxin, alinidine, phenytoin etc.

Arrhythmia classification

abnormal impulse formation
   early afterdepolarizations
      occur in phase 3
      more likely at slow heart rates, long QT interval
      worse with class Ia, Ic and III drugs
   delayed afterdepolarizations
      occur in phase 4
      due to ↑ Ca^{2+}, more likely in fast heart rates
      worse with digoxin, catecholamines, ischaemia, hypercalcaemia

abnormal impulse conduction
   AV block
      three degrees
      worse with ↑ vagal tone, β-blockers, Ca^{2+} channel blockers
   reentry
      area of no conduction adjacent to area of one-way conduction
      circuit long enough to avoid refractory period
      source of tachyarrhythmias
      improved with either increased or decreased conduction

other abnormal conduction pathways
   Wolf-Parkinson-White
   other accessory pathways
b, c, e. Describe the pharmacodynamics and pharmacokinetics of the antidysrhythmic drugs. Describe the side effects and problems associated with the use of antidysrhythmic drugs during anaesthesia.

potassium
↑ plasma [K⁺] causes ↓ Eₘ and ↑ Pₖ
more effect in non-pacemaker cells (↑ Vₘ)
less effect on pacemaker cells

magnesium
acts on Na⁺/K⁺ ATPase, Na⁺, K⁺ and Ca²⁺ channels
mechanism of action uncertain
used in torsade and digoxin toxicity
effective in paediatric acute asthma (25-50 mg/kg of MgSO₄)

adenosine in New Developments (2.B.24)

quinidine
stereoisomer of quinine
pharmacokinetics
high bioavailability
80% protein bound (competes with digoxin)
hepatic metabolism and renal clearance
t₁/₂ β 6 h
IV preparation also used for malaria
pharmacodynamics
α antagonist, antimuscarinic
may cause ↑ AV conduction
    decompensation in AF or flutter due to ↑ ventricular rate
prolonged QT and APD predispose to torsade
nausea, vomiting, cinchonism, ↑ digoxin levels

procainamide
procaine with an amide instead of ester linkage
75% bioavailable
metabolized to N-acetyl procainamide (type III → torsade)
ganglion blocker
negative inotrope
long term SLE syndrome

disopyramide
50% bioavailable
t₁/₂ β 6 h
potent antimuscarinic (full range of atropine effects)
negative inotrope

imipramine
class Ia activity (not used for this purpose)

amiodarone
iodine-containing tertiary amine
pharmacokinetics
high oral bioavailability
concentrated in cardiac tissue
large Vₐ → loading time 15-30 days
t₁/₂ β weeks to months
pharmacodynamics
\(\alpha, \beta\) antagonist, Ca\(^{2+}\) channel blocker (type II and IV)
binds Na\(^+\) channels in the inactive state (type I)
probably blocks K\(^+\) channels (type III)
effects
cardiac
\(\uparrow\) APD, ERP, QT
bradycardia, AV block
adverse
corneal deposits (100%)
pulmonary fibrosis (5-15%)
skin discoloration (5%)
photosensitivity (25%)
neurological problems
hyper- or hypo-thyroidism (5%)
constipation (20%)
hepatocellular necrosis
interactions
\(\downarrow\) clearance of warfarin, theophylline, quinidine, procainamide...
clinical use
effective in most arrhythmias including WPW (\(\downarrow\) accessory conduction)
phenytoin
Na\(^+\) and Ca\(^{2+}\) blocker
\(\downarrow\) automaticity
effective in digoxin toxicity
flecainide
Na\(^+\) channel blocker (type Ic)
suppresses PVCs
caused doubled mortality in CAST trial for asymptomatic PVCs
bretylium
inhibits catecholamine release after initial release \(\rightarrow\) hypotension
prolongs action potential
previously used in resuscitation and for LA toxicity
no longer available in Australia
sotalol
L isomer non selective \(\beta\) blocker
D & L isomers prolong action potential
d. Describe the pharmacological basis of the antidysrhythmic properties of lignocaine, including its pharmacokinetics.
lignocaine
diethyl glycine xylidide
class Ib antidysrhythmic
pharmacokinetics
3% bioavailable orally (tocainide and mexiletine are oral congeners)
\(pK_a\) 7.9
70% bound to \(\alpha_1\) acid glycoprotein
\(t_{1/2,\alpha}\) 8 min
\(V_d\) 1.3 l/kg
hepatic metabolism (E = 68%)
N deethylation, hydrolysis, 3\(^{\prime}\) and 4\(^{\prime}\) hydroxylation
clearance 15 ml/kg/min  
\( t^{1/2} 90 \text{ min} \)
renal excretion

**pharmacodynamics**
- binds \( S_6 \alpha_4 \) domain of voltage-gated Na\(^+\) channel in open state
- rapid release from binding site in inactivated and resting states
- prevents Na\(^+\) flux
- reduces \( V_{\text{max}} \), prolongs QRS
- binds open and inactivated Na\(^+\) channels
- rapid dissociation in resting state, so little effect on normal tissue
- Na\(^+\) channels in tissue with prolonged depolarization stay in inactive state
  - \( \rightarrow \) preferential binding in ischaemic or digoxin toxic tissue
- positive inotrope at low dose
- exacerbates arrhythmias in <10% (good)

**clinical use**
- local anaesthetic use in Local Anaesthetics (2.B.11)
- antidysrhythmic use
  - agent of choice in ventricular arrhythmias
  - loading dose: 1.5 mg/kg followed by 3x0.7 mg/kg at 10 minute intervals
  - infusion: 20-60 µg/kg/min
    - infusion rate depends on clearance (\( \downarrow \) in hepatic disease, CCF)

**adverse effects**
- level (µg/ml)
- effect

<table>
<thead>
<tr>
<th>Level (µg/ml)</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>anticonvulsant, antidysrhythmic</td>
</tr>
<tr>
<td>4</td>
<td>positive inotrope, tinnitus, lightheadedness</td>
</tr>
<tr>
<td>6</td>
<td>vision disturbance</td>
</tr>
<tr>
<td>8</td>
<td>twitching</td>
</tr>
<tr>
<td>10</td>
<td>convulsions</td>
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<tr>
<td>15</td>
<td>coma</td>
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<tr>
<td>20</td>
<td>respiratory arrest</td>
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<tr>
<td>26</td>
<td>cardiac arrest</td>
</tr>
</tbody>
</table>

f. Describe the pharmacological basis of the use of digoxin as an antidysrhythmic and its toxic effects.

digoxin
- glycoside derived from *Digitalis purpurea*
- consists of lactone, steroid and sugars
- lactone and steroid are the active part (aglycone or genin)
- other similar agents: digitoxin and ouabain are not used in Australia

**pharmacokinetics**
- 75% bioavailable (less with certain gut flora)
- 30% protein bound
- \( V_d 6 \text{ l/kg}, \) concentrated in heart, liver and kidney
- renal excretion unchanged
- \( t^{1/2} 40 \text{ h} \)

**pharmacodynamics**
- binds to and inhibits Na\(^+\)/K\(^-\) ATPase pump
- different affinities in different tissues
- binding competes with K\(^+\) (\( \uparrow \) effect with hypokalaemia)
- less negative membrane potential
- reduced activity of Na\(^-\)-dependent pumps (Na\(^+\)/Ca\(^{2+}\) exchanger)

**effects**
- cardiac
  - \( \uparrow \) intracellular Ca\(^{2+}\)
\( \downarrow \text{Na}^+/\text{Ca}^{2+} \) exchange, \( \uparrow \text{Ca}^{2+} \) entry via channels, \( \uparrow \) SR release results in \( \uparrow \) contractility, \( \uparrow \) automaticity, no change in rate, \( \uparrow \) K\(^+\) conductance

\( \downarrow \) AP duration

at high Ca\(^{2+}\) levels, delayed afterdepolarizations occur → bigeminy

\( \uparrow \) toxicity with hypercalcaemia, any arrhythmia

neuro

\( \uparrow \) vagal tone at low dose: \( \downarrow \) HR

CTZ stimulation

vision changes

GIT

nausea, anorexia, vomiting, diarrhoea

other

gynaecomastia

clinical use

IV or oral administration