Antiarrhythmic Pharmacopoeia

Powerful drugs, split into 4 major classes, according to the predominant receptor they effect. Some fit into several classes at once, like sotalol. Some don’t fit at all, owing to the intrinsic weirdness of their actions and the archaic quaintness of this system of classification, introduced in 1970 by EM Vaughan Williams.

**CLASS 1 drugs: Fast Sodium Channel Blockers, “membrane stabilizers”**

These are split into 3 subclasses, organized by binding speed (but, curiously, not in any order).

The classes are 1a, 1b and 1c. From fastest to slowest binding, the order is B, A, C.

Why would you want different speeds? The speed of binding is also the speed of dissociation from the receptor. Many of these drugs only bind to an active receptor. Let's say the heart is going very fast, and the drug is slow to dissociate from the receptor: each time an action potential comes past the cell, more and more channels are going to get blocked. This results in a general slowing of the rate of action potential propagation, and so the QRS interval widens.

**CLASS 1 A: quinidine, procainamide, and disopyramide.**

Used very rarely. Only Disopyramide is available for use in Australia, and the rest have fallen out of favour in 2007. “moderate blockade”

- Block fast sodium channels, thus reduce rate of phase 0 upstroke
- Block repolarising potassium channels, thus prolong repolarisation
- Prolong QRS interval
- Prolong QT interval

Therefore, the length of the action potential is greatly slowed. It takes time for the inactive sodium channels to activate again because the cell takes so long to get below the threshold.

**DISOPYRAMIDE**

...is an oral medication. It produces a rate-dependent slowing of Phase 0. It also slows the action potential duration. That means fewer ventricular ectopics. Everything conducts more slowly with disopyramide, but the non-sodium-channel-based pacemakers fire as per usual. Well, sort of... Disopyramide is also anticholinergic, and so it produces a sinoatrial tachycardia by blocking some of the vagus nerve's effect.

Myocardial contractility will be markedly depressed. Blood pressure will drop, but vascular resistance will rise- which is bad for everyone with poor LV function.

**ADDITIONALLY: THESE DRUGS BLOCK PACEMAKER DEPOLARISING CURRENTS.**

This effect is most pronounced in the His and Purkinje fibers, and ectopic pacemakers.

**Clinical indications:**

- various reentrant or ectopic ventricular or atrial arrhythmias. Affects atrial and ventricular tissue in much the same way. No specific target. By now many better drugs have been developed and so Class 1a agents are no longer first-tier therapies for anything
**CLASS 1 B:** lignocaine, mexiletine.

Fastest blockade; bind to inactive receptors (i.e. during the depolarization period.)

Dissociate quickly, “Mild blockade”

**USED IN TACHYARRHYTHMIAS. Practically no effect at slower heart rates.**

- Block fast sodium channels, thus reduce rate of phase 0 upstroke
- Increase the rate of repolarisation
- Greatest action is on ischaemic, acidotic cells. No effect on the atria.
- Little effect on QT interval

**LIGNOCAINE:** a well known local anaesthetic, delivered intravenously. You will find yourself reaching for the lignocaine when the VT/VF arrest is not going well, and the sotalol is not doing much. If the arrest went well and the patient is still alive, you may be wanting to use a lignocaine infusion to prevent a recurrence. Uniquely, lignocaine suppresses afterdepolarisations.

**MEXELITINE** is an oral medication for the treatment of sustained ventricular arrhythmia, and can actually prevent the torsade de pointes which is associated with QT prolongation. Its pretty much an oral form of lignocaine.

**Clinical indications:**
- Ventricular arrhythmias, especially those associated with digoxin toxicity or recent ischaemia
- Practically useless in AF, flutter or SVT.

**CLASS 1 C:** flecainide and propafenone. Highest level of blockade.

Slowest activity; bind to both active and inactive receptors. Because they dissociate slowly, the effect is greatest at fast heart rates. This is called “USE DEPENDENCE”

**YOU MUST MONITOR QRS PROLONIGATION WITH THESE DRUGS. >50% IS TOXIC.**

- SERIOUSLY block fast sodium channels
- The rate of repolarisation remains unchanged
- Greatly prolong refractory periods- everywhere, including accessory pathways, AV node, atrial and ventricular muscle
- Will precipitate heart failure in people with crappy ventricles.
- Prolong QRS, QT and PR intervals

**Clinical indications:**
- SVT of all sorts. Preventative effect as well as a chance to extinguish the arrhythmia.
**CLASS 2 drugs:** Beta Blockers, anti-sympathetic drugs.

Mainly act on Beta-1 adrenoceptors; also have mild sodium channel blocking properties. Beta-blockade slows the rate of sinus pacemakers, or any ectopic pacemakers. It also increases the refractory period of the AV node, and it will slow conduction of retrograde or anterograde accessory pathways. So if you are in rapid AF, fewer beats will be conducted to the ventricle. It’s just like carotid massage (except carotid massage uses the reverse mechanism and increases parasympathetic input instead of decreasing sympathetic input)

- Increase the refractory period of the AV node, thereby aborting reentrant rhythms which rely on it
- Reduce myocardial oxygen demand, thereby reducing ischaemia
- PR interval is prolonged; QT and QRS are unaffected.

**Clinical indications:**
- AF and flutter: reduce conduction to the ventricles
- Termination of reentrant SVT (also by slowing AV node conduction)
- Termination of ventricular arrhythmias which are related to prolonged QT

**CARVEDILOL** is a bizarre beta-blocker. It also blocks alpha adrenoceptors. It also blocks potassium, sodium and calcium currents. **ADMINISTERED CHRONICALLY,** it increases the number of these channels.

**CLASS 3 drugs:** Potassium channel blockers.

It’s really just SOTALOL and AMIODARONE. Blocking the potassium channels prolongs repolarisation, prolongs the action potential duration and increases the refractory period.

**On ECG, that looks like QT prolongation.**
This may lead to torsade de pointes, and doom.
REMEMBER!! Long QT equals DOOM! Drug induced long QT is made more sinister by bradycardia, hypokalemia or hypomagnesemia.

This means reduced reentry, and slowed conduction

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**Sotalol** is also a beta-blocker with the attendant pro-arrhythmic properties thereof.
When using sotalol long-term, you must monitor the QT interval.

**Amiodarone** is an omni-blocker a’la carvedilol, blocking depolarized sodium channels, potassium channels and some of the adrenoceptors. It’s the least pro-arrhythmogenic of the lot.
When using amiodarone, you must monitor thyroid and liver function; it may also cause pulmonary fibrosis. Its half-life is 25-60 DAYS.

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**CLASS 4 drugs:** **Calcium channel blockers.**

Its really just **VERAPIMIL** and **DILTIAZEM.** Blocking the calcium channels will slow the rate of AV node conduction and prolong the AV refractory period. In the presence of beta blockers, calcium blockade will slow the sinus rate ridiculously, like to 30.

- Decrease automaticity (reduced phase 4 spontaneous depolarization)
- Elevate threshold potential
- Decrease the rate of Phase 0 upstroke
- Lengthen AV node refractory period

Calcium channel blockers depress left ventricular function. Expect the stroke volume to decrease and blood pressure to fall.

**Clinical indications:**
- Reentrant paroxysmal SVT. This role is now held by adenosine, but in the olden days people used to get verapimil IV.

**Unclassed drugs:**

**ADENOSINE**

- Potassium channel agonist
- **best thing ever for terminating paroxysmal SVT;** provided it uses the AV node, and there is no fast accessory pathway. It opens potassium channels in the pacemaker nodes, and thus hyperpolarizes the membrane. This has the effect of prolonging Phase 4, slowing the firing rate. Ventricular myocytes are immune to this effect because the specific potassium channels are not present in those cells.

- **Completely block the AV node**

**CONTRAINDICATIONS:**

- **ACCESSORY PATHWAY!** Adenosine also shortens the refractory period. It can induce atrial fibrillation. If you have WPW or something similar, adenosine might induce ventricular fibrillation.
- **Asthma or severe COPD** (may cause bronchospasm)
- **Sick sinus syndrome**
- **Broad complex tachycardia**
DIGOXIN

- **inhibitor of the Na⁺/K⁺ ATPase**: raises intracellular sodium. Having too much sodium in the cell reduces the activity of the sodium-calcium exchange pump. So, the calcium stays in the cytosol, and the ever-working SERCA calcium pump patiently sweeps it all up into the sarcoplasmic reticulum. **Having more calcium incarcerated within the reticulum is beneficial**: when the cell depolarizes and the calcium-gated calcium channels open, the massive rush of stored calcium causes the myofilaments to contract more powerfully.
- **Most important therapeutic effect is the slowed conduction velocity in the AV node.**

HOWEVER:

Digoxin toxicity has 3 important effects in the Purkinje fibers:

- **less negative resting potential**; therefore some of the fast sodium channels are always closed, the action potential is slowed and if this effect is heterogeneous among ventricular muscle, reentrant arrhythmias may arise.
- **decreased action potential duration** means refractory periods actually shorten, and so there is more risk of an arrhythmia propagating.
- **Enhanced automaticity** because the threshold is nearer (i.e. the resting potential is less negative) and the increased intracellular calcium might trigger **AFTERDEPOLARISATIONS**.
WHY WOULD WE USE THESE INSANELY TOXIC DRUGS?

Why not a 200 joule shock?
Why indeed.

Carotid massage will only resolve those arrhythmias which rely on the AV or SA node. Otherwise, they will only increase the AV block.

ATRIAL FIBRILLATION
The first thing you must decide is whether there is any hemodynamic compromise. If there is, then the treatment of choice is DC cardioversion.
Also add 25000 units of heparin in 45 ml of saline infusion to anticoagulate; the atria of these people tend to become “stunned” and flaccid following a DC shock, which predisposes them to forming clots.

Supraventricular tachycardia.
- get a large bore cannula in, and attach a fast drip.
- Give 6mg adenosine as fast as you can (otherwise it will get metabolized)
- This should give you a few seconds of AV nodal block. You will see the underlying atrial rhythm, and hopefully revert the SVT to sinus.
- Didn’t work? Try 12 mg bolus. And then an 18mg bolus.

ADENOSINE USELESS?
Move onto verapimil.
- give a slow bolus of 5-10 mg IV over about 5 minutes, while monitoring BP constantly. Works best with an arterial line.

Ventricular tachycardia in a conscious patient:
- give sotalol IV, 1.5mg/kg (so, about 100mg for a normal-sized person)
- then, prepare for elective cardioversion. If its not working, give another 0.5mg/kg sotalol. If its still; not working, you need to move on to IV lignocaine as a 1mg/kg bolus, delivered slowly. You may attempt an infusion. This is given as 4mg/minute for the first hour, followed by 2mg/minute thereafter.

Ventricular tachycardia or ventricular fibrillation in an arrest setting
- Immediate DC shock. These are referred to as "shockable rhythms". In contrast, pulseless electrical activity (PEA) and asystole just get adrenaline 1mg every 5 minutes during resus.

- Adrenaline should be given in any arrest, regardless of rhythm. In the case of a shockable rhythm, give it after the 3rd attempt at DC cardioversion.

- For VF/VT, you also give sotalol 1.5mg/kg after the 3rd attempt.
- Once again, try a lignocaine bolus of 1.5mg/kg if nothing is working.
- If the arrest is lasting for longer than 10-15minutes, you may want to give IV bicarbonate, around 50 to 100 mmol. IF the patient is hyperkalemic, you will want to give calcium gluconate before the bicarbonate.
And, finally:

**Torsade de Pointes**

Usually paroxysmal! Will be self limiting, you hope. Or it may degenerate into VF. Either way, just give magnesium 1-2g IV. It works even in people with normal magnesium levels. Keep giving it every 10-15 minutes. Reserve DC cardioversion until last. Lignocaine is useless.

Usually, the cause of this weirdness is a long QT interval; seeing as this interval is proportional to the duration of the whole P-T complex, a slow heart rate will prolong your QT. So something that increases heart rate will be protective against this tachyarrhythmia. Something like isoproterenol, a beta1/beta2 agonist. In effect, this will produce pharmacological overdrive pacing, and hopefully terminate the torsade (especially acquired torsade, such as caused by class 1a drugs or sotalol).