The Pharmacology of Amiodarone and Digoxin as Antiarrhythmic Agents

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The heart contains pacemaker, conduction and contractile tissue. Cardiac arrhythmias are caused by either enhancement or depression of cardiac action potential generation by pacemaker cells, or by abnormal conduction of the action potential. The pharmacological treatment of arrhythmias aims to achieve restoration of a normal rhythm and rate.

The resting membrane potential of myocytes is around -90 mV, with the inside of the membrane more negative than the outside. The main extracellular ions are Na^+ and Cl^-, with K^+ the main intracellular ion. The cardiac action potential involves a change in voltage across the cell membrane of myocytes, caused by movement of charged ions across the membrane. This voltage change is triggered by pacemaker cells. The action potential is divided into 5 phases (figure 1).

Phase 0: Rapid depolarisation

Duration < 2ms

Threshold potential must be reached (-70 mV) for propagation to occur

Rapid positive charge achieved as a result of increased Na^+ conductance through voltage-gated Na^+ channels in the cell membrane

Phase 1: Partial repolarisation

Closure of Na^+ channels

K^+ channels open and close, resulting in brief outflow of K^+ and a more negative membrane potential

Phase 2: Plateau

Duration up to 150 ms

Absolute refractory period – prevents further depolarisation and myocardial tetany

Result of Ca^{++} influx through voltage-sensitive L-type Ca^{++} channels, K^+ efflux and Cl^- influx, with a near balance of ion movement

Phase 3: Repolarisation

Membrane potential returns to resting value

Relative refractory period – supra-normal stimulus required for contraction

Result of increased K^+ conductance and closure of Ca^{++} channels, with a net outward positive current

Phase 4: Resting potential

The resting membrane potential is mainly determined by K+ equilibrium and the Na^+/K^+ ATPase pump (figure 2) maintains ionic concentration gradient and membrane potential at approximately -90 mV by exchanging 3 Na^+ for 2 K^+ using ATP

The sodium-calcium exchanger also trades 1 Ca^{++} from the cell for 3 Na^+ into the cell, using ATP

Figure 1. Myocyte action potential

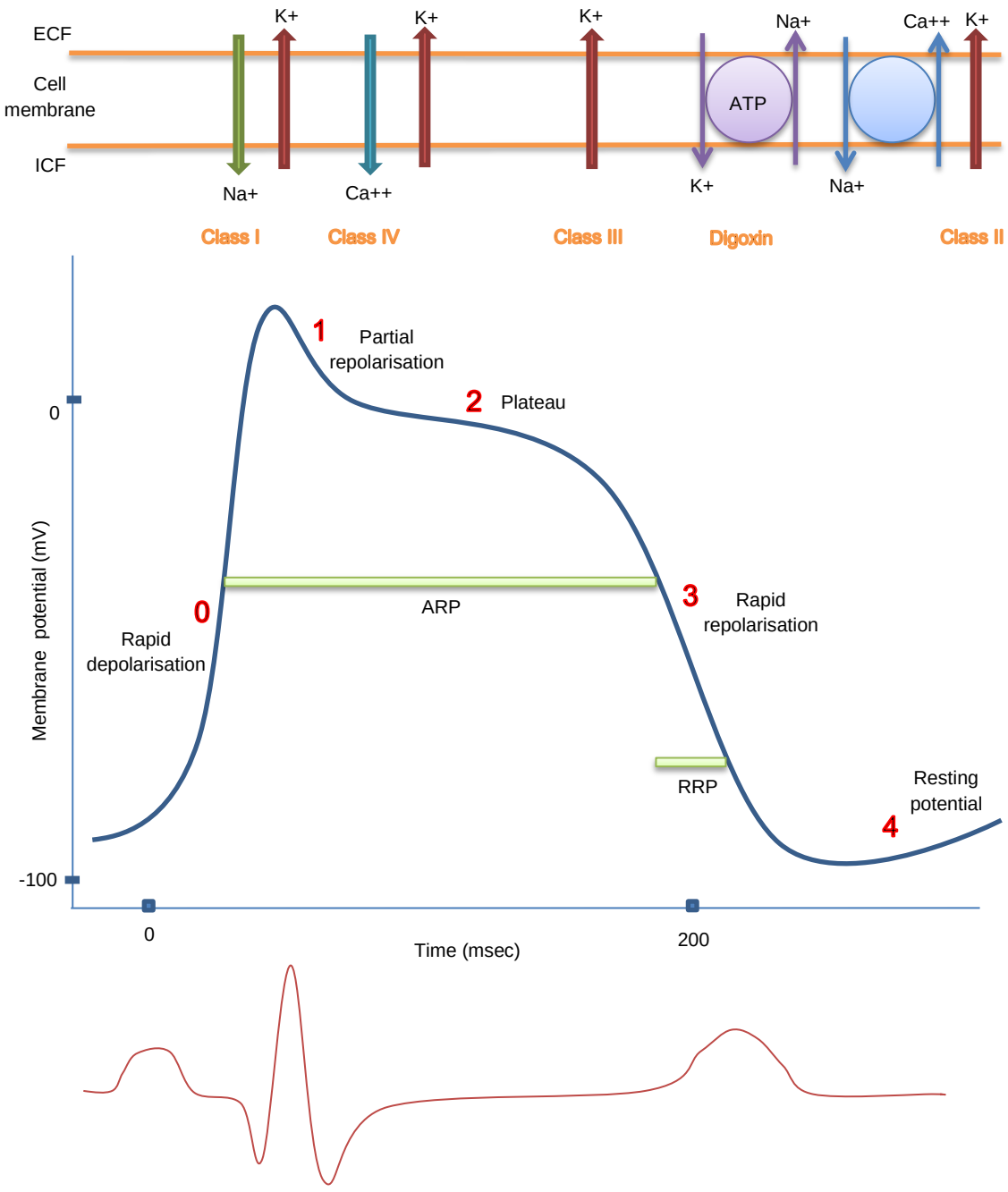
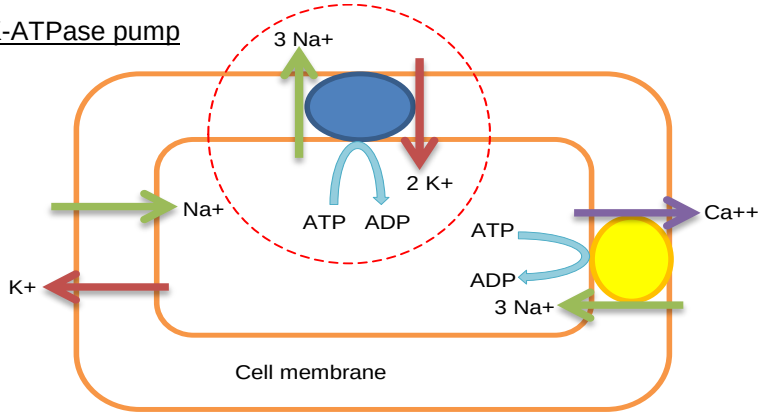


Figure 2. Na-K-ATPase pump



Traditionally antiarrhythmic agents have been classified according to the Vaughan-Williams classification (table 1). This classification does not include agents like digoxin and adenosine.

Some agents also exhibit characteristics that place them in more than one category, e.g. amiodarone (classes Ia, II, III, IV) and sotalol (classes I, II, III). Other methods of classification may include type of rhythm treated or site of action (table 2).

Amiodarone:

Amiodarone is an agent used in the treatment of supraventricular and ventricular tachyarrhythmias, as well as Wolff-Parkinson-White Syndrome. It is classified as a Vaughan-Williams class III antiarrhythmic agent, but it is a complex drug with multiple actions. It blocks K^+ channels, therefore slowing repolarisation and increasing the duration of the action potential.
It also shows sodium and calcium channel blocker properties, and is a non-competitive ß-adrenergic inhibitor. Amiodarone chemically resembles thyroxine and some of its pharmacological effects may be explained by its binding to thyroid receptors.
Amiodarone has multiple side effects and it will affect most patients on chronic treatment. Most side effects are reversible with cessation of treatment, but some side effects have a significant mortality rate e.g. pneumonitis, hepatitis, exacerbation of asthma and congestive cardiac failure.

Digoxin:

Digoxin is a cardiac glycoside that is extracted from the leaves of the foxglove (*Digitalis lanata*) and is widely used in the treatment of atrial fibrillation and atrial flutter, and also in the treatment of cardiac failure.
Digoxin has positive inotropic and negative chronotropic activity due to direct and indirect actions on the heart.
Directly it inhibits the Na^+/K^+ ATPase pump, leading to increased intracellular Na^+ and decreased intracellular K^+ concentrations. The raised intracellular Na^+ concentration leads to reversal of the action of the sodium-calcium exchanger, increasing the exchange of intracellular Na^+ for extracellular Ca^{++}. This results in increased availability of intracellular Ca^{++}, with a positive inotropic effect. The refractory period of the AV node and bundle of His is increased and conduction is therefore slowed down.
Indirectly it increases the release of acetylcholine at myocardial muscarinic receptors. This also increases the refractory period of the AV node and bundle of His, slowing conduction. In addition it may improve baroreceptor sensitivity in patients with cardiac failure and increases renal blood flow.
Digoxin has a narrow therapeutic index and side effects are not uncommon. Cautious dosage determination and monitoring of therapeutic levels are essential. Side effects are also more common in patients with hypokalaemia, as digoxin competes with K^+ ions for the same binding site on the Na^+/K^+ ATPase pump.

The basic pharmacological characteristics of amiodarone and digoxin are summarised in table 3.

Classification of antiarrhythmic agents

Table 1.

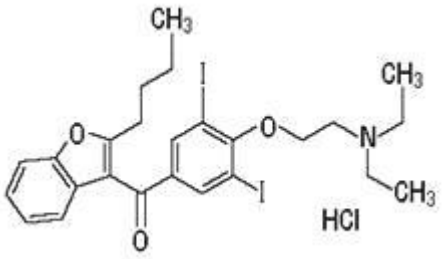
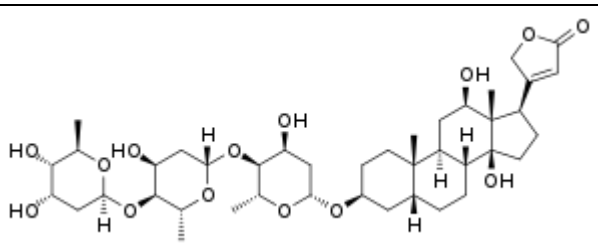
Vaughan-Williams	Site	Drug examples	Action	AP	HR	PR	QRS	QT	EA	CV	RP
Class Ia	Na channel blockade	Quinidine Procainamide Disopyramide	Slow depolarisation ++	↑		↑	↑	↑	↓	AV↑↓ CS↓	↑
Class Ib	Na channel blockade	Lidocaine Phenytoin Mexiletine Tocainide	Slow depolarisation +	↓	↔	↔	↔	↔↓	↓	AV↔ CS↔↓	↑↓
Class Ic	Na channel blockade	Flecainaide Propafenone	Slow depolarisation +++	↔	↔	↑	↔↑	↔↓	↓	↓	↑
Class II	ß - adrenergic blockade	Propanolol Carvedilol Metoprolol	AV nodal blockade		↓	↑	↔	↔↓	↓	AV↓ CS↔	AV↑ CS↔
Class III	K channel blockade	Amiodarone	Slow repolarisation	↑	↓	↑	↑	↑	↓	↓	↑
		Sotalol Bretylium Dronedarone Ibutilide			↓	↑	↔	↑	↓	AV↓	↑
Class IV	Ca-channel blockade	Verapamil Diltiazem	AV nodal blockade		↓	↑	↔	↔	↓	AV↓ CS↔	AV↑ CS↔
Other		Digoxin			↓	↑	↔	↓	↑	AV↓ CS↔	AV↑ CS↓
		Adenosine				↑			↓	AV↓ CS↔	AV↑ CS↔
		Magnesium							↓		

AP=action potential, HR=heart rate, EA=ectopic automaticity, CV=conduction velocity, AV=AV node, CS=conduction system (His-Purkinje and ventricular), RP=refractory period

Table 2

Site of Action	Drug examples
Sinus node and Atrium	ß -blockers Digoxin Amiodarone Quinidine Procainamide Disopyramide Verapamil
Atrio-ventricular node	ß-blockers Digoxin Ca-channel blockers Flecainaide Propafenone
Accessory Pathway	Amiodarone Disopyramide Procainamide Flecainaide
Ventricle	Amiodarone Quinidine Procainamide Disopyramide ß -blockers Lidocaine Mexiletine Phenytoin

Table 3

	Amiodarone	**Digoxin**
Formula	C25H29I2NO3	C41H64O14
Chemical structure		
Chemical name	(2-{4-[(2-butyl-1-benzofuran-3-yl)carbonyl]-2,6-diiodophenoxy}ethyl)diethylamine	(3Beta,5B,12B)-3-[(0-2,6-dideoxy-B-D-ribo-hexopyranosyl-(1 to 4)-0- 2,6-dideoxy-B-D-ribo-hexopyranosyl-(1 to 4)-2,6 dideoxy-B D-ribo-hexopyranosyl)oxy]-12,14-dihydroxycard-20(22)-enolide
Description	Iodinated benzofuran derivative	Sterol lactone + sugar
Classification	Vaughan-Williams Class III antiarrhythmic agent (also exhibit actions of classes Ia, II, and IV)	Cardiac glycoside
Mechanism of action	**Blocks myocardial calcium, potassium and sodium channels** → prolongation of cardiac action potential and refractory period **Inhibits alpha- and beta-adrenergic receptors** → reduction in sympathetic stimulation, negative chronotropy, and ↓ myocardial oxygen demands **Vasodilation** due to ↑ release of nitric oxide and cyclooxygenase-dependent relaxing endothelial factors Inhibition of Cytochrome P450 3A4, 1A2, 2C9, 2D6, 3A7, 2A6, 3A5	**Binds to a site on the extracellular aspect of the Na^+/K^+ ATPase pump and inhibits its action** → ↑ in intracellular Na^+ The ↑ Na^+ gets exchanged for Ca^{++} → ↑ intracellular concentrations of Ca^{++} → activation of contractile proteins (actin, myosin) → ↑ inotropy **Direct action on atrioventricular node** → ↓conduction velocity Due to its effects on intracellular calcium concentrations, digoxin may induce apoptosis of tumour cells via a pathway involving mitochondrial cytochrome c and caspases 8 and 3
Formulations	Oral and intravenous Tablets 100 and 200 mg Intravenous 50 mg/ml, 150 mg/100 ml, 360 mg/200 ml	Oral and intravenous Tablets 0.125, 0.25, 0.5 mg Capsules 0.05, 0.1 or 0.2 mg equivalent to 0.0625, 0.125, and 0.25 mg in tablet form. Elixir 0.05 mg/ml. Intravenous 0.1 mg/ml or 0.25 mg/ml
Stability and storage	Store tablets at room temperature Protect from heat, moisture, and light Light protection is not necessary upon administration Amiodarone Hydrochloride 0.6 mg/ml in dextrose 5% in water is stable for five days at room temperature. Solutions containing < 0.6 mg/ml of amiodarone hydrochloride in dextrose 5% in water are unstable and should not be used	Store tablets at room temperature Protect from heat, moisture, and light
Administration	IV: concentrations >2 mg/mL should be administered via a central venous catheter Initial infusion rate should not exceed 30 mg/min Inline 0.22 micron filter should be used	IV doses must be infused over a minimum time period of 5 minutes

	IO: used in emergency situations	
Reconstitution	Dilute with dextrose 5% in water to a concentration of 1 - 6 mg/mL	Dilute with 4 fold or greater volume of 0.9% sodium chloride solution or dextrose 5% in water
Administration incompatibility	Aminophylline, Cefazolin Sodium, Heparin sodium, Sodium bicarbonate, Cefamandole Nafate, Mezlocillin Sodium, Floxacillin, Digoxin	Dobutamine, Doxapram, Amphotericin B Cholesteryl sulphate, Amiodarone, Fluconazole, Foscarnet, Insulin, Propofol
Indication	**IV** - initiation of treatment and prophylaxis of frequently recurring **ventricular fibrillation and hemodynamically unstable ventricular tachycardia in patients refractory to other therapy** **PO** - treatment of life-threatening recurrent ventricular fibrillation and recurrent hemodynamically unstable ventricular tachycardia	Treatment and management of congestive cardiac insufficiency, arrhythmias and heart failure
Therapeutic uses	As above Treatment and recurrence prevention of supraventricular arrhythmias refractory to conventional treatment, especially supraventricular tachycardia associated with Wolff-Parkinson-White syndrome, also, atrial fibrillation, paroxysmal atrial fibrillation, atrial flutter and ectopic atrial tachycardia	As above **Treatment of choice for controlling rapid ventricular rate in patients with atrial fibrillation or flutter** Treatment of established or paroxysmal atrial fibrillation, atrial flutter or paroxysmal atrioventricular junctional rhythm with a fast ventricular rate Treatment of cardiac failure in combination with other agents Prophylactic use to prevent arrhythmias and congestive heart failure in patients with heart disease without failure during certain stressful situations (surgery, severe illness, pregnancy) Termination of pregnancy Treatment of malignancy (experimental)
Dose	Steady-state concentrations of 1 to 2.5 mg/L have been associated with antiarrhythmic effects and acceptable toxicity following chronic oral therapy **PO**: 800-1600 mg daily (divided doses) for 1/52, then 600-800 mg dly for 1-3 weeks, then 100-400 mg dly **IV**: Loading dose - 150 mg over the first 10 minutes (15 mg/min), followed by 360 mg over the next 6 hours (1 mg/min) Maintenance - 540 mg over the remaining 18 hours (0.5 mg/min) During cardiac arrest 300 mg or 5mg/kg (paediatric dose) is used	Dosage should be based on lean or ideal body weight Therapeutic levels are between 0.6 and 2.6 nmol/l and requires monitoring Loading dose PO or IV - administer 50% initially; then may cautiously give 25% 8hly x2 with careful assessment of clinical response and toxicity before each dose **PO**: Loading dose 10-15 mcg/kg Maintenance 3.4-5.1 mcg/kg/day **IV**: Loading: 8-12 mcg/kg total Maintenance: 2.4 to 3.6 mcg/kg/day Loading dose only used in AF, not required in CCF Switching from IV to PO: IV dose (mcg) x 1.25 = PO dose (mcg)
Monitoring	Serum hepatic enzyme concentrations should be monitored at regular intervals Serum electrolyte levels, thyroid, eye and respiratory function periodically	Measure serum digoxin levels 6-10 hours post administration Monitor serum electrolytes and creatinine periodically
Dose modification		Decrease dose in renal impairment
Half life	Elimination $t^{1/2}$ =4h-54 days Biological $t^{1/2}$ = **58 days** (range 15-142 days)	Elimination $t^{1/2}$ = 34-44 hr with normal renal function Biological $t^{1/2}$ = **3.5 - 5 days**
Bioavailability	Slowly and variably absorbed from the GI tract 22 - 86%	Absorption occurs from small intestine ↓ by co-administration of food, malabsorption syndromes, antacids, and ↓ GI motility

		Elixir 70% - 85% Capsules 90% - 100% Tablets 60% - 80%
Protein binding	**>96%**	**25%**
Distribution	**Volume of distribution: adults 1.3-65.8 l/kg** Widely distributed in adipose tissue, liver, lung, spleen, skeletal muscle, bone marrow, adrenal glands, kidneys, pancreas, bile, testes, semen, saliva, lymph nodes, myocardium, thyroid gland, skin, and brain Placental transfer - foetal level 10 - 25% of maternal plasma level Breast milk level substantially higher than maternal plasma level	**Volume of distribution: adults, 7-8 l/kg, neonates 10 l/kg, infants 16 l/kg** Vd ↓ in renal disease, hypothyroidism, quinine therapy and the elderly (↓ muscle mass) 65% of the absorbed dose distributed to skeletal muscle Widely distributed in heart, kidneys, intestine, stomach and liver Lowest concentrations are in plasma, adipose tissue and brain Freely cross the placenta with similar foetal and maternal plasma concentrations Maternal concentrations in plasma and breast milk are similar.
Metabolism and excretion	**Hepatic - extensively metabolised** via CYP2C8, also possible metabolism in the intestinal lumen and/or GI mucosa Mainly biliary excretion Negligible excretion in urine	Hepatic (independent of cytochrome P-450 system) Bacterial metabolism in large intestine **50%-80% of dose excreted unchanged in urine**, 9-13% excreted via faeces and bile
Active metabolites	Major metabolite of amiodarone is Desethylamiodarone (DEA), which also has antiarrhythmic properties and a $t^{1/2}$ = 36 (14-75)	Digoxin undergoes stepwise cleavage of the sugar moieties to form digoxigenin-bisdigitoxoside, digoxigenin-monodigitoxoside, and digoxigenin; with progressively decreasing cardioactivity Other metabolites are cardio-inactive
Clearance	90-158 mL/h/kg (single dose IV of 5 mg/kg over 15 min) 1.9 ml/min/kg (range: 1.4-2.5 ml/min/kg)	Renal clearance 191 ml/min
Contraindications	Known hypersensitivity Cardiogenic shock Sinus node dysfunction associated with sinus bradycardia Second- or third-degree AV block Bradycardia causing syncope, except with functioning artificial pacemaker Porphyria	Known hypersensitivity Ventricular fibrillation
Overdose	Occur with serum level 2.5 mcg/mL	Occur with serum level > 2 ng/mL Toxicity partly due to loss of intracellular potassium **CVS**: Atrial tachycardia, atrial fibrillation, atrial flutter, ventricular tachycardia , ventricular fibrillation, bigeminy, junctional premature complexes, progressive bradyarrhythmias, heart block, heart failure **GI**: Nausea, vomiting, salivation, abdominal pain **CNS**: Headache, dizziness, vertigo, agitation, seizures, visual disturbance, drowsiness, muscle weakness, confusion, coma, respiratory failure
Treatment of overdose	Supportive management, ALS Activated charcoal, cholestyramine Sodium bicarbonate may reverse cardiac depressant effects caused by inhibition of the fast sodium channel Magnesium sulphate for polymorphic ventricular tachycardia Avoid Class 1a agents	**Antidote = Anti-digoxin Fab antitoxin** (for significant toxicity only) Supportive management, ALS Induced vomiting if <30 min since ingestion and patient alert and stable Activated charcoal, cholestyramine Class 1b agents for tachyarrhythmias Atropine or PM for bradyarrhythmias Correct electrolytes

		Avoid calcium
Adverse reactions	**Pulmonary** – occurs in 10-17%, potentially fatal (10%) - interstitial pneumonitis, hypersensitivity pneumonitis, pulmonary fibrosis, exacerbation of asthma, haemoptysis **Neurological** - peripheral neuropathy, proximal muscle weakness, visual disturbances in 10%, asymptomatic corneal deposits in almost all patients, rarely reports of nystagmus, ischemic optic neuritis, optic neuropathy, papilledema, corneal degeneration, scotoma, lens opacities, ocular discomfort and macular degeneration **Endocrine** – hypothyroidism in 2-4%, rarely hyperthyroidism, abnormalities of liver function test results in 3-55%, rarely, severe hepatic injury (hepatitis, hepatocellular necrosis, cirrhosis), non-infectious epididymitis or epididymo-orchitis and/or scrotal pain, gynecomastia, hyper/hypoglycaemia **CVS** – arrhythmias (brady and tachy) in 2-5%, hypotension in 16% (IV), new or worsening cardiac failure in 2-3%, phlebitis **Coagulation** - abnormalities in 1-3%, rarely severe thrombocytopenia **GI** - nausea, vomiting, constipation and anorexia in 25%, abdominal pain, abnormal salivation and abnormal taste in 1-3% **Dermatological** – photosensitivity in 10%, pigment deposition → blue-gray discoloration of the skin, rash and hair loss in <1, rarely toxic epidermal necrolysis and psoriasis Stevens-Johnson syndrome in <2% of patients receiving the drug IV **Malignancy** - possible association between amiodarone and an increased risk of cancer, especially in males	**GI** – anorexia, nausea and vomiting, abdominal pain, diarrhoea, constipation in 1-10%, very rare - intestinal ischemia, intestinal haemorrhagic necrosis **Neurological** - visual disturbances, headache, facial pain, weakness in 1-10% **Psychiatric** – depression, apathy, anxiety, psychosis, confusion, delirium, hallucination in 0.1-1% **Endocrine** – gynecomastia **CVS** - arrhythmias (brady and tachy) in 1-10%, **Dermatological** – Rashes in 1-10%
Hypersensitivity	Rare Angioedema and anaphylactic shock have been reported	Rare Usually within 6-10 days after initiating therapy. Rashes, usually accompanied by eosinophilia Urticaria, pruritis, fever Facial, angioneurotic, or laryngeal oedema; Alopecia of the scalp, desquamation Shedding of finger and toe nails Rarely, thrombocytopenic purpura
Drug interactions	↑ **levels of other agents** e.g. Digoxin, Phenytoin, Procainamide, Flecainide, Cyclosporine, Quinidine, Theophylline, Sildenafil Ledipasvir, Sofosbuvir – severe bradycardia Warfarin – serious ↑ in PT Simvastatin - ↑risk of rhabdomyolysis Potentially serious adverse	↑ **levels**: Amiodarone, Quinidine, Verapamil, Nifedipine, Diltiazem, Nicardipine, Flecainide, Propafenone Prazocin , Calcium IV, Spironolactone, Furosemide, Indomethacin, short course Ibuprofen Diazepam, Heparin, Methyldopa, Trazodone, Tolbutimide, Erythromycin, Tetracycline, Metoclopramide, Hydroxychloroquine, Cyclosporine, Trimethoprim

	cardiovascular effects have occurred in some amiodarone treated patients undergoing general anaesthesia, e.g bradycardia and heart block resistant to atropine and adrenaline, these patients may require temporary pacing perioperatively ↓**levels**: Activated charcoal, Cholestyramine	↓**levels**: Sulfasalazine, Neomycin, Penicillamine, Aminosalicylic acid, Activated charcoal, Cholestyramine
Food interactions	Grapefruit juice significantly ↑ levels	↓ absorption with co-administration of food Hawthorn ingestion increases risk of arrhythmias
Special precautions	Avoid during pregnancy and breastfeeding Use with caution in patients receiving calcium channel blockers and/or beta-adrenergic blockers Use with caution in patients receiving agents known to prolong QT interval IV administration not recommended for use in the paediatric population due to potential for adverse male reproductive tract development and the preservative benzyl alcohol has been associated with the potentially fatal "gasping syndrome" in neonates	Use with extreme caution during pregnancy and breastfeeding Use with extreme caution, if at all, in patients with idiopathic hypertrophic subaortic stenosis because increased obstruction to left ventricular outflow may result Incidence of toxicity increased by hypokalaemia, hypomagnesaemia, hyperkalaemia, hypernatraemia and alkalosis Risk factors for toxicity include hypothyroidism, renal failure, myocardial infarction, myocarditis, chronic constrictive pericarditis, hypoxia, severe pulmonary disease, recent cardiac surgery, severe bradycardia, severe heart failure, sick sinus syndrome, ventricular tachycardia, ventricular premature contractions, Wolff-Parkinson-White syndrome and reduced muscle mass It should be avoided or used very cautiously in these patients

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