PC3301
Pharmacokinetics of Amiodarone

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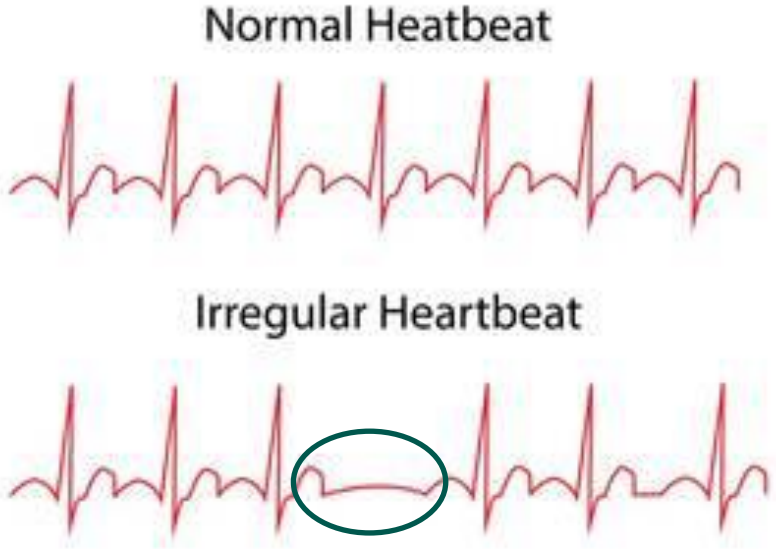
Amiodarone Introduction

Antiarrhythmic medication used to treat and prevent a number of types of irregular heartbeats conditions. This Includes

- ➔ Ventricular Tachycardia
- ➔ Ventricular Fibrillation
- ➔ Atrial Fibrillation
- ➔ Paroxysmal supraventricular tachycardia



Brief History

- ➔ First made in 1961 for chest pain
- ➔ Taken out from the market in 1967 due to its side effects
- ➔ 1974 it was reintroduced
- ➔ World Health Organisation List of Essential Medicines [14].

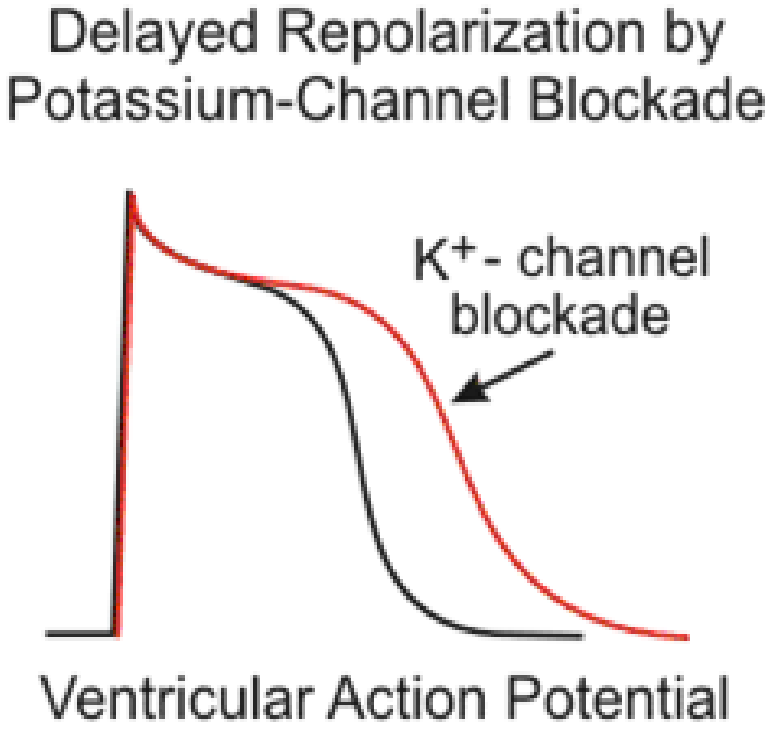
Basic Pharmacology

➔ Vaughan-Williams Class III antiarrhythmic agents

Class	Examples	Mechanism
Ia	Quinidine Procainamide	Na^+ channel blockers (intermediate association/dissociation)
Ib	Lidocaine Phenytoin	Na^+ channel blockers (fast association/dissociation)
Ic	Flecainide Propafenone	Na^+ channel blockers (slow association/dissociation)
II	Propranolol Metoprolol	Beta blockers (propanolol also shows some class I action)
III	Amiodarone Sotalol	K^+ channel blockers (sotalol is also a beta blocker; amiodarone has Class I, II, III, and IV activity)
IV	Verapamil Diltiazem	Ca^{2+} channel blockers
V	Adenosine Digoxin	Work by unknown mechanisms (direct nodal inhibition)

Basic Pharmacology

- ➔ Prolongs action potential (phase 3) duration and refractory (unexcitable) period in all cardiac tissues
- ➔ It decreases automaticity, prolongs AV conduction, and decreases the automaticity of fibres in the Purkinje system
- ➔ It primarily blocks potassium channel and can also block sodium (class I effect) and calcium channels (class IV effect)
- ➔ It also has weak noncompetitive beta-adrenergic inhibitor activity (Class II effect)



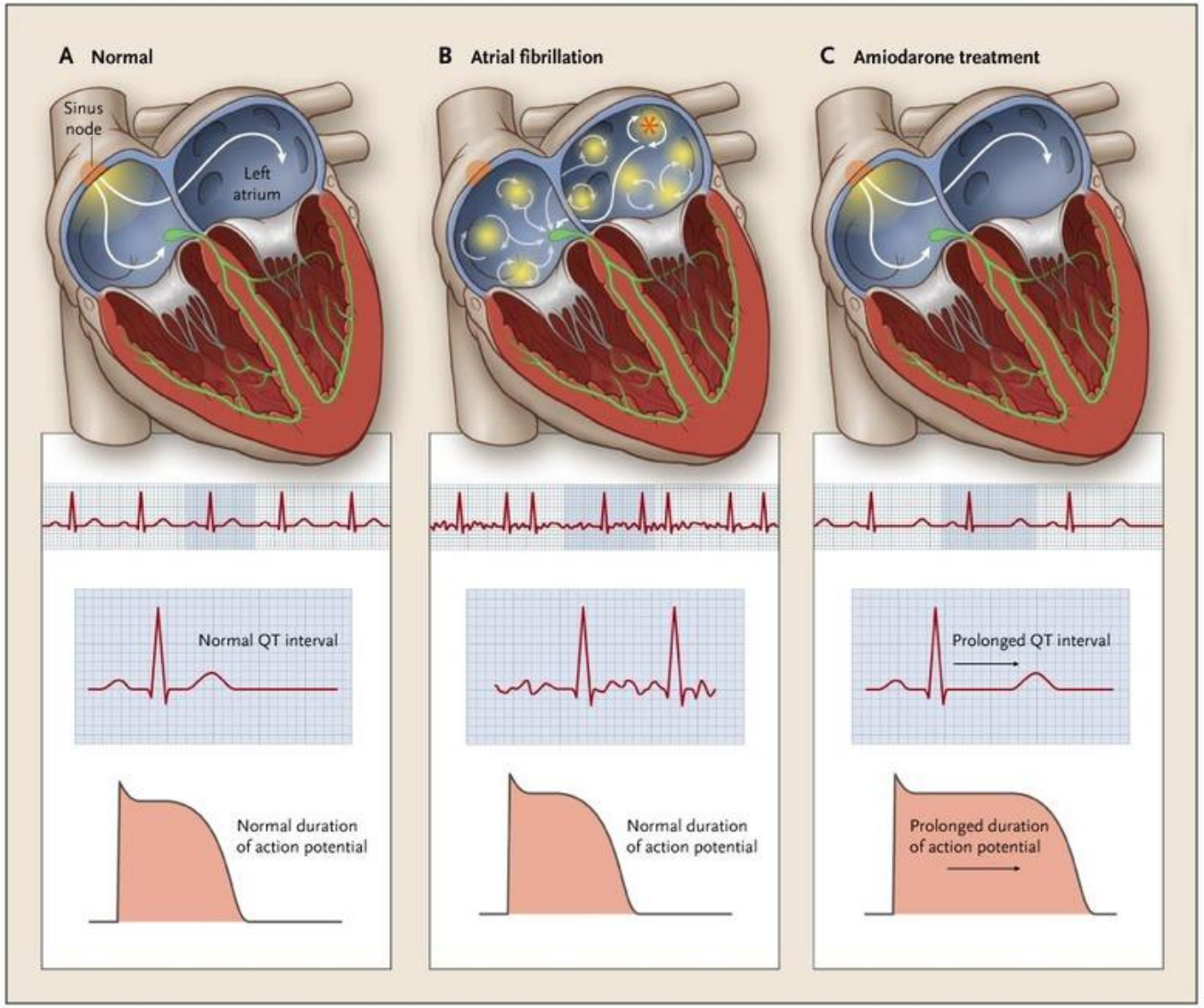
https://www.nzgp-webdirectory.co.nz/Cardiac+Action+Potential++Vaughan+Williams+Classification+of+Antiarrhythmic+Agents.html

Side Effects

Frequency	Side Effects
Common (> 1%)	Nausea and vomiting, constipation, anorexia, taste disturbance, thyroid dysfunction, fever, photosensitivity, skin pigmentation (blue-grey), corneal microdeposits, headache, sleep disturbances, pulmonary toxicity, moderate bradycardia, hypotension (IV)
Rare (<0.1%)	Hepatotoxicity (may be fatal), optic neuropathy, bronchospasm, acute respiratory distress syndrome, heart failure, torsades de pointes, severe bradycardia, allergic rash, thyroid dysfunction

Clinical Uses

- ➔ Serious tachyarrhythmias such as supraventricular, nodal and ventricular tachycardias, atrial flutter and fibrillation, ventricular fibrillation
- ➔ Especially when other therapies are not effective
- ➔ Treatment usually initiated in hospital



Dose and Administration

Oral Therapy

Loading, oral 200 mg 3 times daily for 1 week, followed by 200 mg twice daily for 1 week.

Maintenance, oral 100–200 mg once daily (400 mg daily may be required, especially for ventricular arrhythmias)

Intravenous Injection

Emergency, IV 150–300 mg over 1–3 minutes (monitor clinical signs and ECG very closely).

Loading, IV 5 mg/kg over 20 minutes – 2 hours.

Maintenance, IV 15–20 mg/kg over 24 hours (maximum 1.2 g in 24 hours)

Clinical Preparations

tab, 100 mg (scored), 30, *Aratac*, *Cordarone X*

tab, 200 mg (scored), 30, *Aratac*, *Cordarone X*, *Rithmik*

inj, 50 mg/mL, 3 mL, 6, *Cordarone X*

Drug Interactions

- Drug interactions often results from its inhibition of CYP2C9, CYP2D6, and CYP3A4

In particular Amiodarone can:

- Need to reduce Digoxin dose by 50%
- Increase plasma concentration of Phenytoin
- Increase warfarin anticoagulant effect by inhibiting metabolism of warfarin (warfarin toxicity!)

It is important to:

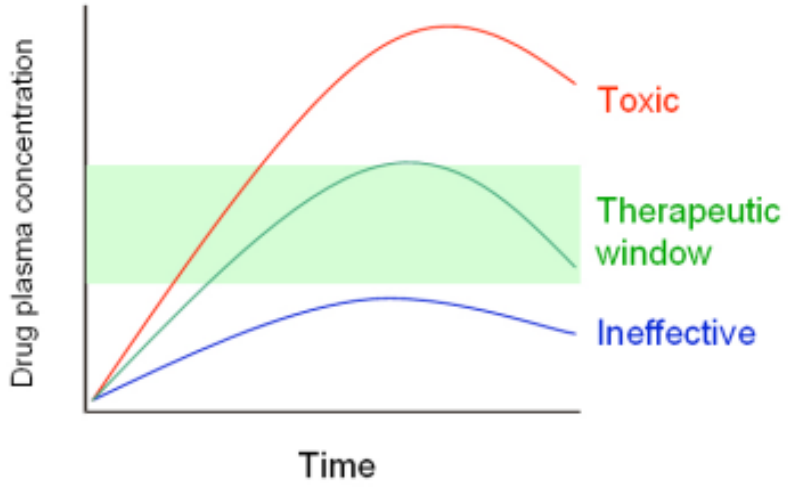
- Avoid eating grapefruit and drinking grapefruit juice while taking amiodarone

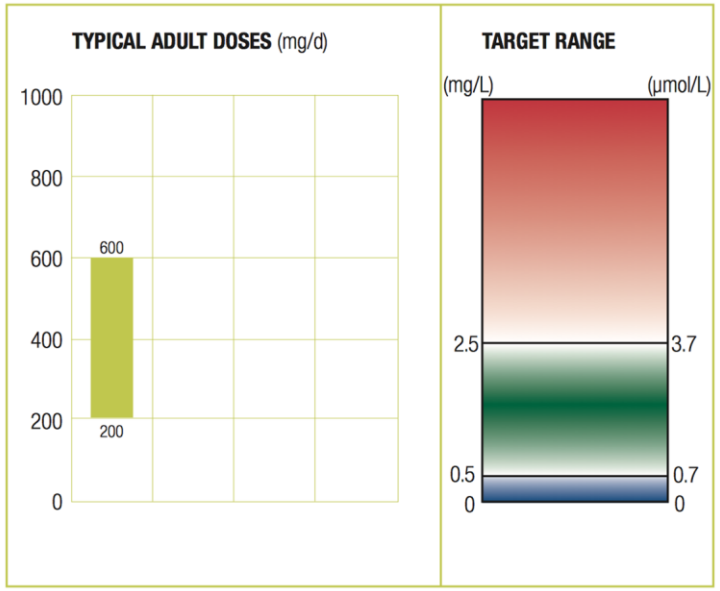
Table. **Amiodarone drug interactions**

Drug	*Result*
Anticoagulants	↑ prothrombin time
Beta blockers	Additive beta blockade
Calcium channel blockers	↑ risk of AV block
Cholestyramine	↓ amiodarone concentration
Cimetidine	↑ amiodarone concentration
Cisapride	QT prolongation
Cyclosporine	↑cyclosporine concentration
Dextromethorphan	↑dextromethorphan conc.
Digoxin	↑ digoxin concentration by as much as 70%
Disopyramide	QT prolongation
Fentanyl	Hypotension, bradycardia
Flecainide	↑ flecainide concentration
Phenytoin	↑ phenytoin conc.; ↓ amiodar. conc.
Lidocaine	Rare reports of bradycardia, seizures
Methotrexate	↑ methotrexate conc.
Procainamide	↑ procainamide or NAPA concentrations
Quinidine	↑ quinidine concentration
Quinolones	↑ risk of arrhythmias
Theophylline	↑ theophylline conc.
Rifamycins	↓ amiodarone conc.

Therapeutic Drug Monitoring

- ➔ Therapeutic range of amiodarone is between 0.5–2.5 mg/L
- ➔ Maximum effect of dosage change is not seen until 1–3 months or more.
- ➔ Toxicity may be likely at levels >2.5 mg/L but adverse effects can still occur within the therapeutic range.
- ➔ Most patients do not need monitoring. But TDM can be useful
  To monitor compliance and toxicity
  Differentiate treatment failure from poor adherence or suboptimal dosing





Precautions

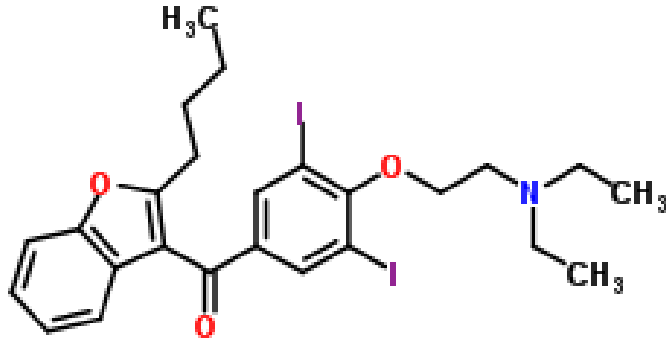
- ➔ Thyroid function- hypo- or hyperthyroidism
- ➔ Electrolyte maintenance- hypokalaemia, hypocalcaemia, hypomagnesaemia
- ➔ Hepatic function- hepatotoxicity
- ➔ Cardiac function- QT prolongation

Overdose

- Toxicity more likely in patients with underlying heart disease or electrolyte disorders.
- The onset of toxicity may be delayed due to poor absorption.
- No common clinical signs but there may be
  Bradycardia
  ECG changes (QT prolongation)
  Idioventricular rhythm
- Treatment with beta- adreno stimulants or glucagon given and temporarily withdraw or gastric lavage (extreme circumstances)

Chemical properties

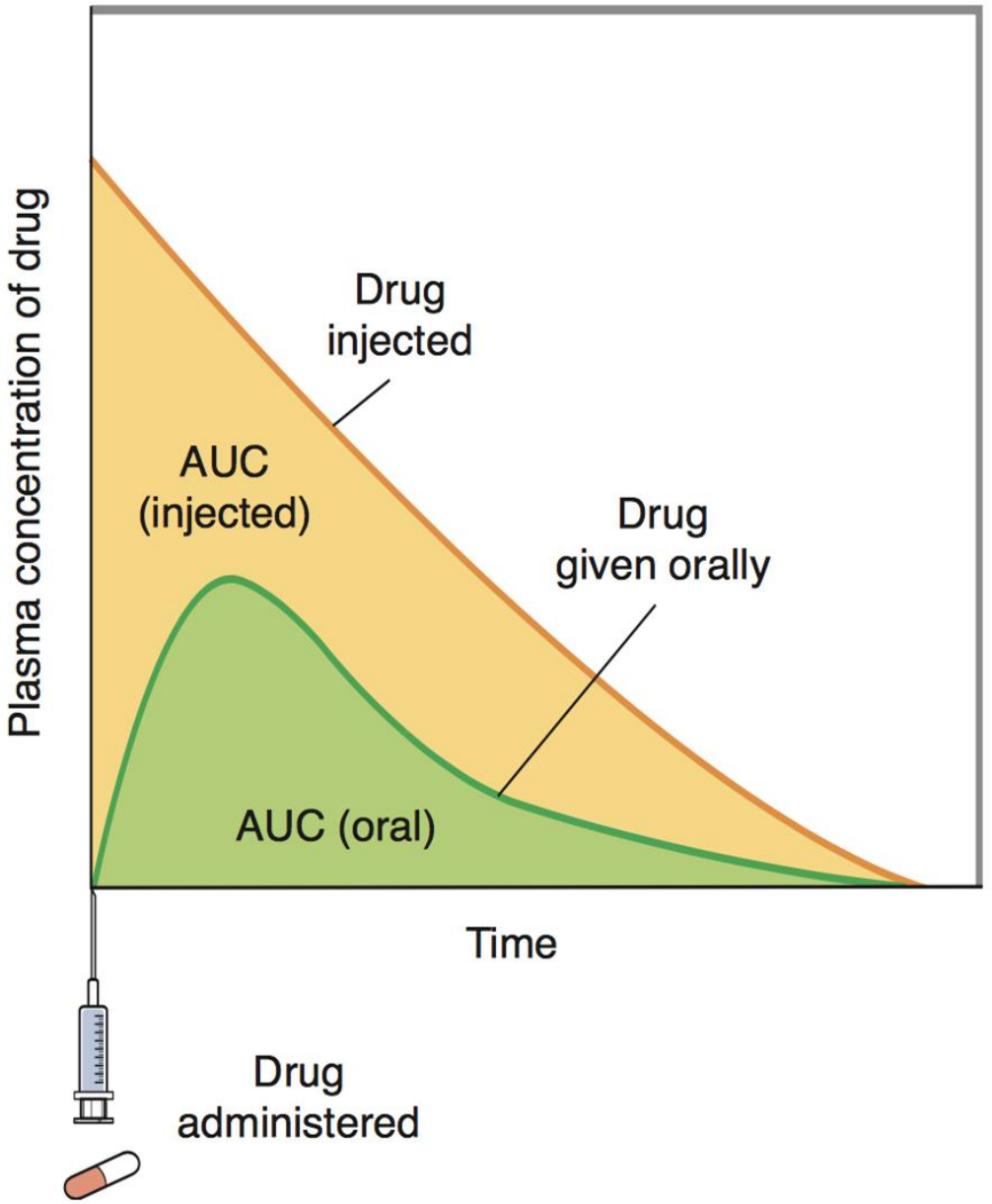
- ➔ C25H29I2NO3
- ➔ Molecular Weight: 645.32 g/mol
- ➔ Composition: C (46.53%), H (4.53%), I (39.33%), N (2.17%), O (7.44%)
- ➔ pKa: 8.47
- ➔ logP: 7.64
- ➔ LogD at pH 7.4 (blood pH): 6.53
- ➔ LogD at pH 6.5 (urine pH): 5.68
- ➔ LogD at pH 4.6 (stomach pH): 4.29



Pharmacokinetics

Absorption

- ➔ GI tract absorption is unpredictable and erratic
- ➔ The bioavailability of amiodarone is between 22% and 86%.
- ➔ Maximum plasma level concentrations are achieved approximately 3-7 hours following a single dose.
- ➔ Pharmacological effects are between 1-3 weeks after administration, even when an initial loading doses is utilized.
- ➔ Interaction with food increases both the amount and speed of absorption



Distribution

- ➔ Very lipophilic so high volume of distribution
- ➔ Averaging approximately 66 L/kg
- ➔ Range between 0.9 and 148 L/kg
- ➔ Long time to reach stable plasma levels
- ➔ Around 30 to 70 percent absorbed and rest taken up by tissue
- ➔ It is 96% plasma bound

Metabolism

- ➔ Metabolism of amiodarone occurs by the CYP450 group of enzymes in particular the CYP3A4 and CYP2C8 (major)
- ➔ Its extensively metabolized in the liver (under 1% unchanged in urine), and can affect the metabolism of numerous other drugs
- ➔ The major metabolite of amiodarone is desethylamiodarone
- ➔ Its inhibited by grapefruit juice, leading to elevated serum levels of amiodarone and various drugs that can also increase and decrease the levels of amiodarone in blood

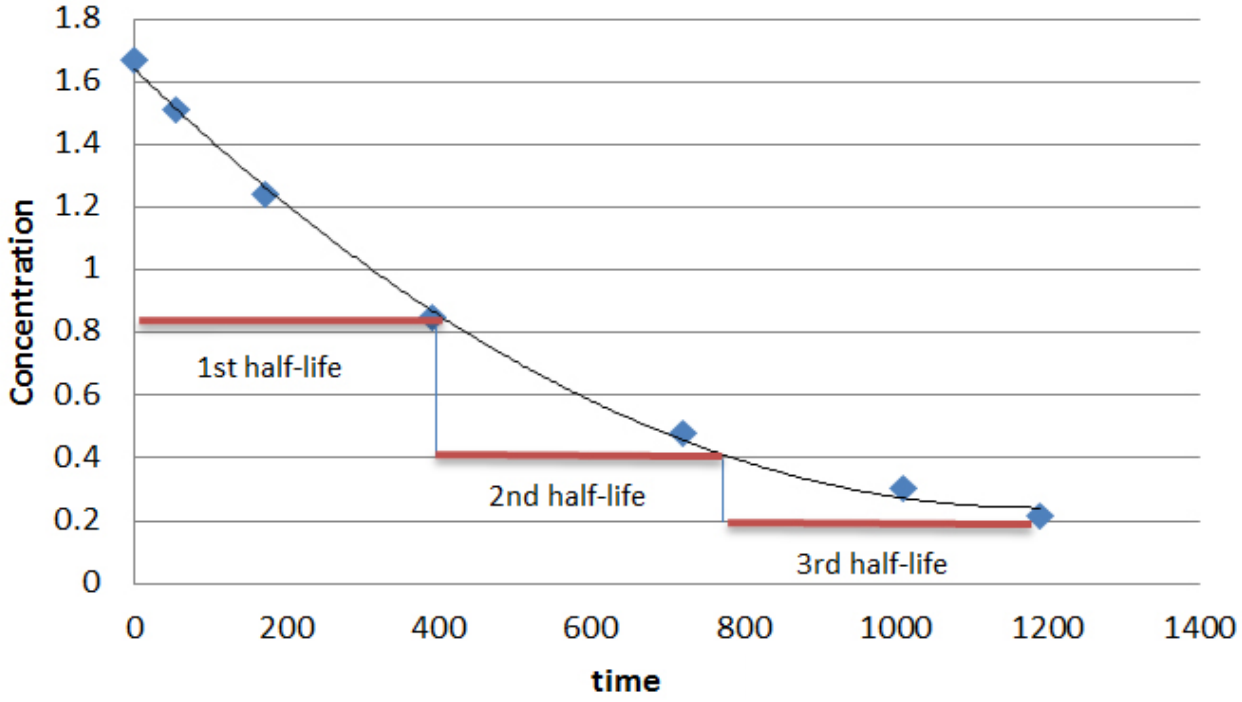
Elimination

- ➔ Eliminated largely by metabolism
- ➔ Desethylamiodarone is the only metabolite identified in the plasma; no data are available on its possible pharmacological activity.
- ➔ Clearance

  90-158 mL/h/kg [Healthy with a single dose IV (5 mg/kg over 15 min)
  100 mL/h/kg [Normal subjects > 65 yrs]
  150 mL/h/kg [younger subjects]
  220 and 440 mL/h/kg [patients with VT and VF]

Half-Life

The Half-life of Amiodarone is extensive and inconsistent. For long term use half life is between 14 to 59 days but has shown to vary between 14-110 days, if the patient has been using the drug for a chronic condition



Special Populations

Elderly

Use in Children

Renally Impaired

An Adult with Obesity

Hepatic Impairment

Pregnancy and Breastfeeding

Case Study

RM is a 71 year old female (weight 71kg; height 164cm) with a past medical history of coronary artery disease. She was admitted to the cardiovascular intensive care unit. She had atrial fibrillation two days after her coronary artery bypass grafting. She was started on a loading regimen of amiodarone **150 mg IV bolus**, followed by **1 mg/min for 6 hours**, and was switched to and has been on an amiodarone infusion of **0.5 mg/min for 36 hours**.

Calculate Mrs RM's plasma concentration of amiodarone

➔ at the end of the **6-hour infusion at a rate of 1 mg/min**; and

➔ at the end of the **36-hour infusion at a rate of 0.5 mg/min**.

What Do We Already Know?

$$Vd = 66\frac{L}{kg} \times 71kg = \mathbf{4686L}$$

$$t\frac{1}{2} = 59\ days = \mathbf{1416h}$$

$$k = \frac{0.693}{t\frac{1}{2}} = \frac{0.693}{1416hrs} = \mathbf{4.894 \times 10^{-4} h^{-1}}$$

$$D_{(bolus)} = 150mg$$

$$Cp_0 = \frac{D_{(bolus)}}{Vd} = \frac{150mg}{4686L} = \mathbf{0.0320 mg/L}$$

Cp- Plasma Concentration
k- elimination rate constant
t(1/2)-half-life
Vd-volume of distribution

Question 1

Calculate plasma concentration at the end of the 6-hour infusion at a rate of 1 mg/min.

Cp at start of 6 hours from IV bolus.

$$Cp_0 = C_0 e^{-kt}$$

$$0.0320e^{-4.894\times10^{-4}\times6} = \mathbf{0.0319mg/L}$$

Cp after 6 hours at end of IV infusion (t=6hours) with 1 mg/min infusion

$$k_0 = 1\frac{mg}{min} = 60\frac{mg}{h}$$

$$Cp_6 = \frac{k_0}{kVd}\left(1 - e^{-kt}\right)$$

$$Cp_6 = \frac{60}{4.894 \times 10^{-4} \times 4686}\left(1 - e^{-(4.894\times10^{-4})(6)}\right)$$

$$Cp_6 = 26.163 \times 0.00293$$

$$\boldsymbol{Cp_6 = 0.0767mg/L}$$

$$Total\ Cp_6 = 0.0319\frac{mg}{L} + 0.0767\frac{mg}{L} = \mathbf{0.1086}\,\boldsymbol{\frac{mg}{L}}$$

Question 2

Calculate plasma concentration at the end of the 36-hour infusion at a rate of 0.5 mg/min.

Cp (6) = 0.1086mg/L

Cp at start of 36 hours infusion

$$Cp_0 = C_0 e^{-kt}$$

$$0.1086e^{-4.894\times10^{-4}\times36} = \mathbf{0.1067mg/L}$$

Cp after 36 hours at end of IV infusion (t=36hours) with 0.5 mg/min infusion

$$k_0 = 0.5\frac{mg}{min} = 30\frac{mg}{h}$$

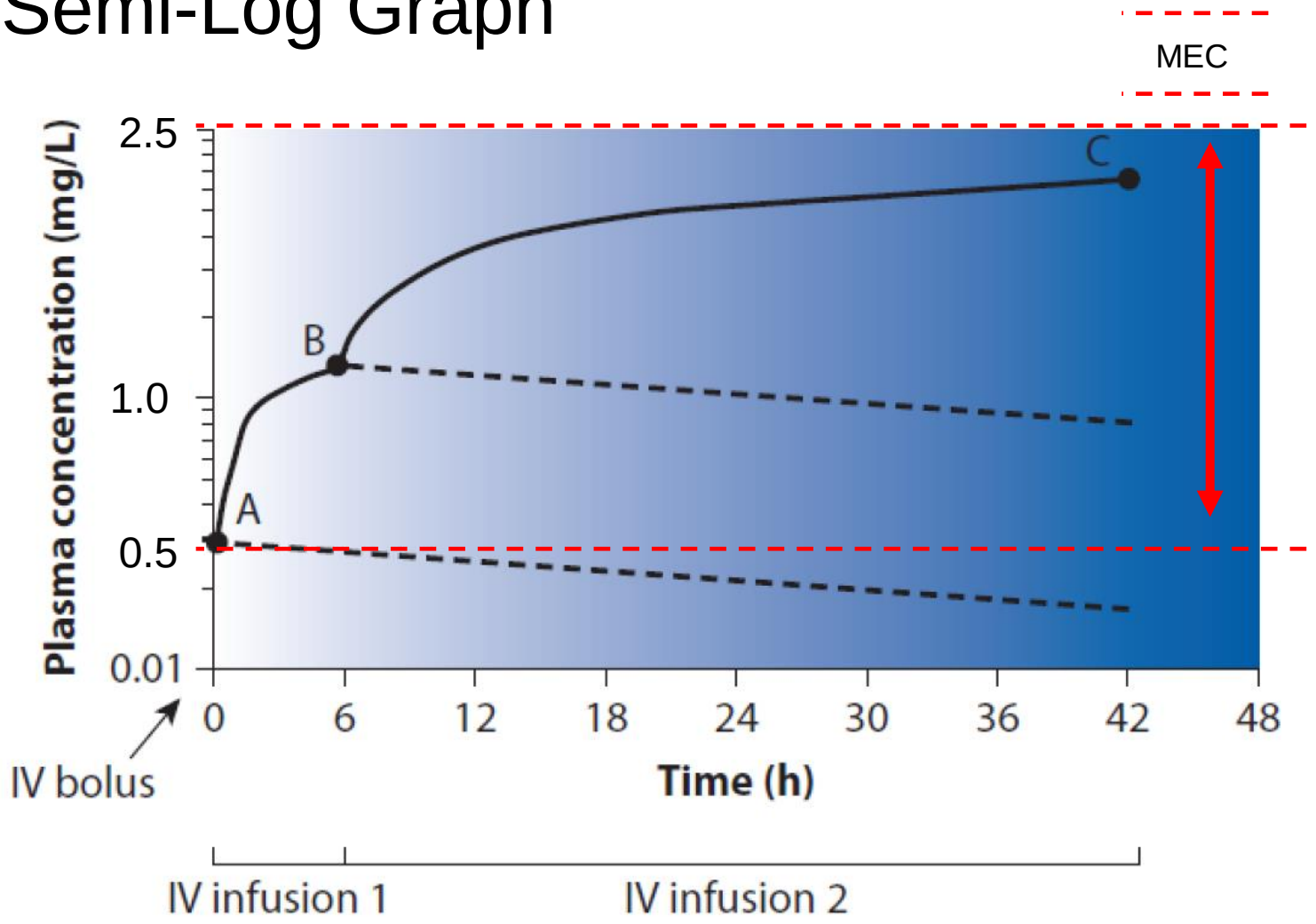
$$Cp_{36} = \frac{k_0}{kVd}\left(1 - e^{-kt}\right)$$

$$Cp_6 = \frac{30}{4.894\times10^{-4}\times4686}\left(1 - e^{-(4.894\times10^{-4})(36)}\right)$$

$$13.08 \times 0.0175 = 0.229mg/L$$

$$Total\ Cp = 0.1067 + 0.229 = \mathbf{0.3357}\frac{\boldsymbol{mg}}{\boldsymbol{L}}$$

Semi-Log Graph



- ➔ Therapeutic range of amiodarone is between 0.5–2.5 mg/L
- ➔ Toxicity may be likely at levels >2.5 mg/L
- ➔ IV bolus dose is given to achieve Cmax immediately
- ➔ IV infusion at different rates are given to keep the Cp within therapeutic range and avoid toxicity.
- ➔ Oral doses are given when MEC is steady following IV admin. Initial high oral dose and then low maintenance dose to ensure steady Cp is maintained (not shown in the graph)

References

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