THE NORTHERN HOSPITAL

AMIODARONE

"The Oxen of Geryon", (detail), Greek Chalcidian black figure amphora from Southern Italy, depicting the Tenth Labour of Heracles, c. 540 - 530 B.C, Bibliothèque Nationale de France.

Zeus was overjoyed when his son was born, he wanted him to be a great hero and protector of the mortals, however his wife Hera always loathed any of the offspring of her husband's - all too frequent - "liaisons". She would do everything in her power to hinder, and hopefully destroy them, and her loathing applied most especially to the great Heracles. When Heracles had grown to manhood, he was given the hand in marriage of Megara, the beautiful daughter of the king of Thebes, Creon. Heracles had many children with Megara, but then Hera in a rage of jealousy cast a powerful spell over him that sent him into a paranoid rage. Thinking he was surrounded by enemies on all sides he slew all of his children. When he realized what he had done he was inconsolable and went to the Oracle of Delphi to seek a means of penance and atonement. The hero was ordered to go into the service of King Eurystheus of Mycenae, as a common slave. The evil and dishonorable King Eurystheus was in fact a protégé of Hera, and so it seems that Hera herself had malignly influenced the sacred Oracle! Hera ordered King Eurystheus, to send Heracles on a suicide mission. Eurystheus, in his extreme eagerness to please Hera, did better than that - he ordered Heracles to ten suicide missions - which he later, extended to twelve, by trickery that showed a sick genius for manipulating contract law, which would have made his fortune in a later era! And so it was that Heracles was condemned to his famous twelve labours.

King Eurystheus was seriously perturbed! Heracles had just completed his ninth "impossible" labour, and Eurystheus had only three labours left with which he could send Heracles to his doom, thus fulfilling his pledge to the goddess Hera. For the Tenth task he would have to assign Heracles to a truly impossible task - and he had just the mission in mind. For Heracles' seventh task, King Eurystheus had commanded him to capture the terrifying Cretan Bull, which Heracles had achieved without any apparent due difficulty. But now he would command Heracles to capture an entire herd of cattle, and single handedly bring them back to Mycenae. But this was only to be the beginning of the task! The herd of cattle that he had in mind belonged to a monstrous three headed giant called Geryon, who was very fond of his oxen, and would not take it well should they go missing! And as if this was not enough, Geryon lived on a very far distant island called Erythea, beyond the edge of Spain and the known world, a region where no mortal, or demigod for that matter, had ever set foot in. Further; Geryon's herd was constantly watched over by his ever vigilant cowherd Eurytion and his terrifying two headed dog Orthrus, the younger sibling to the even more terrifying three headed dog, Cerberus, who guarded the gates of the underworld.

Heracles happily accepted the impossible challenge, and immediately set out on his long journey. He would face many dangers as he trekked through far distant and uncharted lands, killing many monstrous creatures that tried to devour him along the way. Eventually he reached the end of the world. In recognition of his achievement he decided to erect a magnificent monument so that future generations would know that the great Heracles had been the first to reach this point. He fashioned two great mountains one on either side of a narrow isthmus of the Mediterranean Sea which led to the vast Ocean that surrounded the earth, and within which was situated the island of Erythea. These mountains that straddle the isthmus, became famous as the "Pillars of Heracles". With the help of Apollo, Heracles was able to reach Erythea in a golden boat. He quickly located Geryon's herd and sized up the situation. He ambushed the watchful cowherd Eurytion and killed him with an arrow. Orthrus rushed at Heracles, but he swiftly killed

the fearsome dog with another well aimed shot from his bow. Then with great difficulty he managed to round up Geryon's entire herd of cattle, and juggling all sorts of obstacles eventually drove them to his golden boat. But just at the point he thought he was safe, an enraged Geryon suddenly appeared in full battle dress, brandishing three immense spears! Heracles fought the giant for many hours, eventually bringing him down with three well aimed arrows - one for each head! By this time the cattle had again scattered all over the island and Heracles had to round them all up once again. He then drove them all into his boat and sailed back to Spain. From Spain he still had many adventures, including being attacked by Ligurians as well as Cacus another three headed monster, who lived in a cave and tried to make off with a number of the finest oxen. Needless to say Heracles killed the dreadful Cacus, for the impertinence of trying to steal "his" cattle! He continued on his long journey all the while desperately trying to keep the difficult animals together. On the way he founded the cities of Pompeii and Herculaneum (named after him) - but both would later be destroyed by a great volcanic eruption. On the Island of Sicily the champion boxer Eryx, stole one of the oxen, and Heracles had to go three rounds with him to get it back. He did go three rounds, then of course, killed him. After a number of other adventures Heracles finally managed to get all the cattle back to an astonished King Eurystheus in Mycenae. The King was very embarrassed and dreaded having to break the news to Hera that Heracles despite his best laid evil plans had succeeded yet again. Though he very much coveted Geryon's magnificent beasts, he also very much feared the wrath of the goddess and so he had every single last one of the animals brought to Hera's temple and had them sacrificed to her, which did in the end manage to somewhat placate her.

When we use amiodarone to do battle with an acute arrhythmia, we have confidence, like Heracles, that we can control the situation in the short term. However the story is a much more frustrating one over the longer journey! Just as Heracles faced many perils and frustrations on the long journey home, so do we face our own in the long term use of amiodarone! Heracles did manage to get his cattle home in the end, though sadly with amiodarone and its multitude of obstacles in the form of adverse reactions such a long-term happy ending is not quite so anticipated!

AMIODARONE

Introduction

Amiodarone is the most effective antiarrhythmic drug available.

In most countries (including Australia), amiodarone is the most commonly prescribed antiarrhythmic apart from drugs such as digoxin and beta blockers.

Amiodarone is primarily a **Class III antiarrhythmic agent**, though it does have some antiarrhythmic activity from the other three Vaughn-Williams classes as well.

Amiodarone is used to treat paroxysmal supraventricular tachyarrhythmias, ventricular fibrillation and ventricular tachycardia.

In the ED it is used intravenously for:

- The control of supraventricular tachyarrhythmias:
    - ♥ Either for **rate control** or **reversion to sinus rhythm**
- Sustained VT
- In ALS protocols for VF

In the outpatient setting although amiodarone is orally effective, it is not generally recommended for minor rhythm disturbances because of its toxicity. It is a difficult and challenging drug to use in the longer term. This is because of its very prolonged half-life and because of its multiple adverse effects.

See also separate document on amiodarone overdose (in Toxicology folder)

Chemistry

Amiodarone is an antiarrhythmic drug with structural similarities to **thyroxine.**

It also has a significant iodine component. Each amiodarone 200 mg tablet contains organic iodine approximately **75 mg** and, in the steady state, metabolism of amiodarone 300 mg yields iodine **9 mg/day,** well in excess of the highest normal dietary intake.

Preparation

Tablets: 100 mg, 200mg.

Ampoules: 150 mg / 3 ml ampoules.

Mechanism of Action

Electrophysiological effects on electrical conduction

These include:

- Decreases sinus node and junctional automaticity
    - ♥ It decreases sinus automaticity by reducing the slow diastolic depolarisation gradient in the nodal cell.
    - ♥ This is a direct effect and is not mediated through the sympathetic or parasympathetic system.
- Slows atrioventricular (AV) conduction
- Slows abnormal bypass tract conduction
- Prolongs refractory period of myocardial tissues (atria, ventricles, AV node and bypass tracts).

Antiarrhythmic activity:

Amiodarone is primarily a **class III antiarrhythmic** agent but its activity actually includes all four of the classic Vaughan Williams mechanisms of action, namely:

- Sodium channel blockade (class I activity)
- Mild beta blocking action (class II activity)
- Potassium channel blockade (class III activity
- Some calcium channel blockade (class IV activity)

Pharmacokinetics

Administration:

- Amiodarone is given orally or by nasogastric tube or IV.

    However amiodarone is incompletely and erratically absorbed following oral administration.

    Absolute bioavailability ranges from approximately 20 to 85% with extensive intersubject variation.

    IV administration can be via peripheral line or a central line.

Distribution:

- Amiodarone is highly protein bound
- Amiodarone appears to accumulate in adipose tissue and in highly perfused organs (lung, bone marrow, adrenals, liver, pancreas, heart, spleen and kidney).
- Amiodarone and its desethyl metabolite are secreted in breast milk.

Metabolism:

- Amiodarone is metabolized in the liver.

  Its principal metabolite, is desethylamiodarone. This metabolite is reported to have a longer half-life than amiodarone. Its activity is unknown.

  It is believed that most of the drug is excreted via the liver and gastrointestinal tract by biliary excretion. There may be some hepatic recirculation.

- Renal excretion of the amiodarone is minimal.
- The half-life of amiodarone is very long and with chronic oral dosing can be from 14 to 110 days, but is usually in the range of 15 to 60 days.

Pharmacodynamics

1. Increases coronary blood flow
2. Reduces myocardial oxygen consumption without altering cardiac output.
3. Produces an atropine resistant bradycardia which is dose dependent and proportional to the spontaneous heart rate.
4. Antagonistic to catecholamines and sympathomimetic agents without causing ß-adrenergic blockade.
5. Electrophysiologic effects:

   - Prolongs action potential duration of atrial and ventricular muscle and, to a lesser degree, of Purkinje fibres, without altering the resting membrane potential.
   - Depressant effect on maximum rate of repolarisation.
   - **Strong anti-fibrillatory action.**
   - Does **not** significantly depress the spontaneous diastolic depolarisation of Purkinje fibres.

Indications

Indications include:

1. Atrial tachyarrhythmias for either rate control or reversion to sinus rhythm:
    - Supraventricular tachycardias
    - AF with rapid ventricular response
    - Atrial flutter with rapid ventricular response
2. VT for reversion to sinus rhythm:
3. VF for reversion to sinus rhythm, or increasing the chance of a successful defibrillation.
    - Amiodarone is included in current **ALS protocols.**

Contraindications/ Precautions

1. Conduction abnormalities:
    - Sinoatrial block
    - Second or third degree AV block (unless a functioning pacemaker is in place).
    - Bifascicular or trifascicular conduction disorders, unless a permanent functioning pacemaker is in place.
2. Significant bradycardia
3. Hypotension
4. Thyroid dysfunction:
    - Amiodarone is contraindicated in patients with evidence or a history of thyroid dysfunction.
5. Drug interactions:
    - **Combined therapy with other antiarrhythmic drugs may induce serious proarrhythmic effects such as torsades de pointes**

- Amiodarone can enhance digoxin toxicity by increasing plasma concentrations of digoxin. It may do this by displacing digoxin from tissue binging sites.

Pregnancy

Amiodarone is a class C drug with respect to pregnancy.

Class C drugs are those drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Specialized texts should be consulted for further details.

Amiodarone and its major metabolite, may cause **abnormal thyroid function** and **bradycardia** in the fetus.

Breast feeding

Amiodarone should not be used in breast feeding mothers.

Adverse Effects

Adverse acute effects with IV use may include:

1. Hypotension:
   - This is the most common adverse effect seen with amiodarone.
   - Slowing the rate of administration can help
2. Severe bradycardia:
   - Drug related bradycardia should be treated by discontinuing amiodarone.
3. Conduction delays:

Adverse effects with chronic oral dosing may include:

1. Ophthalmic:
   - Optic neuritis:

     This will require amiodarone withdrawal.
   - Corneal micro-deposits:

     These occur in the lower 1/3 of the cornea and are detected by slit lamp examination.

The deposits are dose dependent and regress with reduction or termination of treatment.

They are considered to be a storage phenomenon, benign in nature, cause minimal symptomatology and their development is prevented or reduced by the use of methylcellulose or sodium-iodine heparinate eye drops.

Ophthalmological monitoring for the development and progress of the deposits is advocated.

2. Thyroid Function Disturbances:

Amiodarone may cause thyroid dysfunction via its iodine content, leading to **both** excess or deficient function.

Thyroid function disturbances are more common in patients with **preexisting or latent** thyroid disease.

- **Hypothyroidism**

Or

- **Hyperthyroidism** [1]

When patients taking amiodarone have high thyroxine (T4) concentrations with normal thyroid stimulating hormone (TSH) concentrations, this is generally benign and requires no treatment.

The severe form of hyperthyroidism that can develop during, or for some months after, **long-term** amiodarone treatment is clinically diverse, with poor correlation between biochemical and clinical severity.

Serum T4 and triiodothyronine (T3) concentrations are elevated and TSH is suppressed.

Weight loss and myopathy can be extreme in the life-threatening form of the disorder.

A distinction between type 1 and type 2 amiodarone-induced hyperthyroidism has been made, (type I due to excess iodine, type II due to a destructive thyroiditis).

Response to antithyroid drugs may be poor, but some forms of this disorder (e.g. type 2) respond to high-dose glucocorticoids.

3. Dermatological:

- Photosensitivity:
    - ♥ This is relatively common

      It can usually be alleviated by the use of sunscreens (with a high Sun Protection Factor) and suitable clothing.
- Bluish skin discoloration and slate-grey facial pigmentation have been reported.
- Erythema, facial flushing and hair loss have also occurred.

4. Neurological:
    - Peripheral neuropathies:

      This is usually reversible on withdrawal of the drug.

5. Liver Function:
    - Regular monitoring of hepatic function is warranted.
    - Elevation of liver enzyme levels occur quite commonly and in some cases are asymptomatic.
    - Reduction in dosage should be considered as the hepatic changes are often dose dependent.

6. Cardiovascular:
    - All patients treated with amiodarone develop sino-atrial slowing which is dose-dependent and proportional to the spontaneous heart rate.
    - Prolongation of the QT interval or QRS interval
    - U-waves and deformed T-waves may occur on ECG because of fixing of amiodarone in myocardial tissue. These particular signs are not signs of intoxication and administration may be continued.
    - **Like all antiarrhythmic agents, amiodarone may also occasionally have paradoxical proarrhythmic effects**

7. Respiratory:

   Two main types of toxic pulmonary reaction are recognized:

- An acute inflammatory pneumonitis, which can develop early or late, is reversible if the drug is withdrawn early and may respond to corticosteroids

- A chronic fibrosis form associated with prolonged exposure, which is less reversible.

Regular chest X-ray should be performed routinely in patients undergoing **long-term** therapy or when diagnosis is suspected.

Dosing

Patients receiving intravenous administration must be on continuous ECG monitoring.

Only dextrose 5% should be used for dilution and infusions.

For VF:

- **Amiodarone 300 mg IV over 1-2 minutes after the 3rd defibrillation shock**

- **If unhelpful a further dose of 150 mg IV over 1 -2 minutes may be given.**

For sustained VT or atrial tachyarrhythmias [1]

- **5 mg/kg is the loading dose over 20 to 30 minutes**

  More generally 150 to 300 mg IV infusion, over 20 to 30 minutes is used.

Followed by:

- **15-20 mg/kg bodyweight given over 24 hours.**

  Or more generally 900 mg IV infusion over 24 hours (if required) -

  The maximum daily dose in 24 hours is 1200 mg

  Compatible only with 5 % dextrose

Oral dosing;

Occasionally amiodarone is used orally for the ongoing prophylactic treatment of tachyarrhythmias

Dosing is as follows: [1]

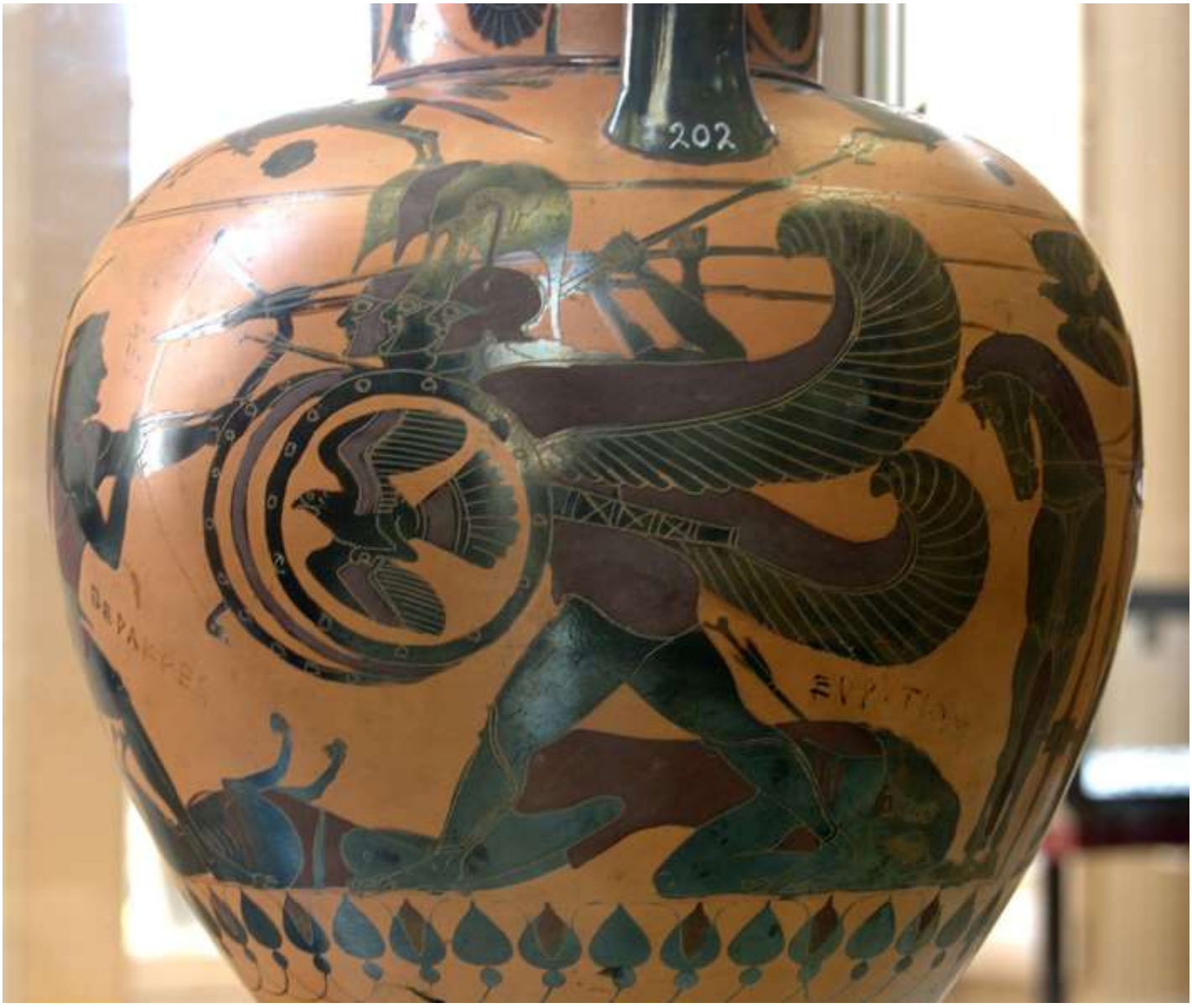
- Amiodarone 200 to 400 mg orally, 3 times daily for 1 week

Then

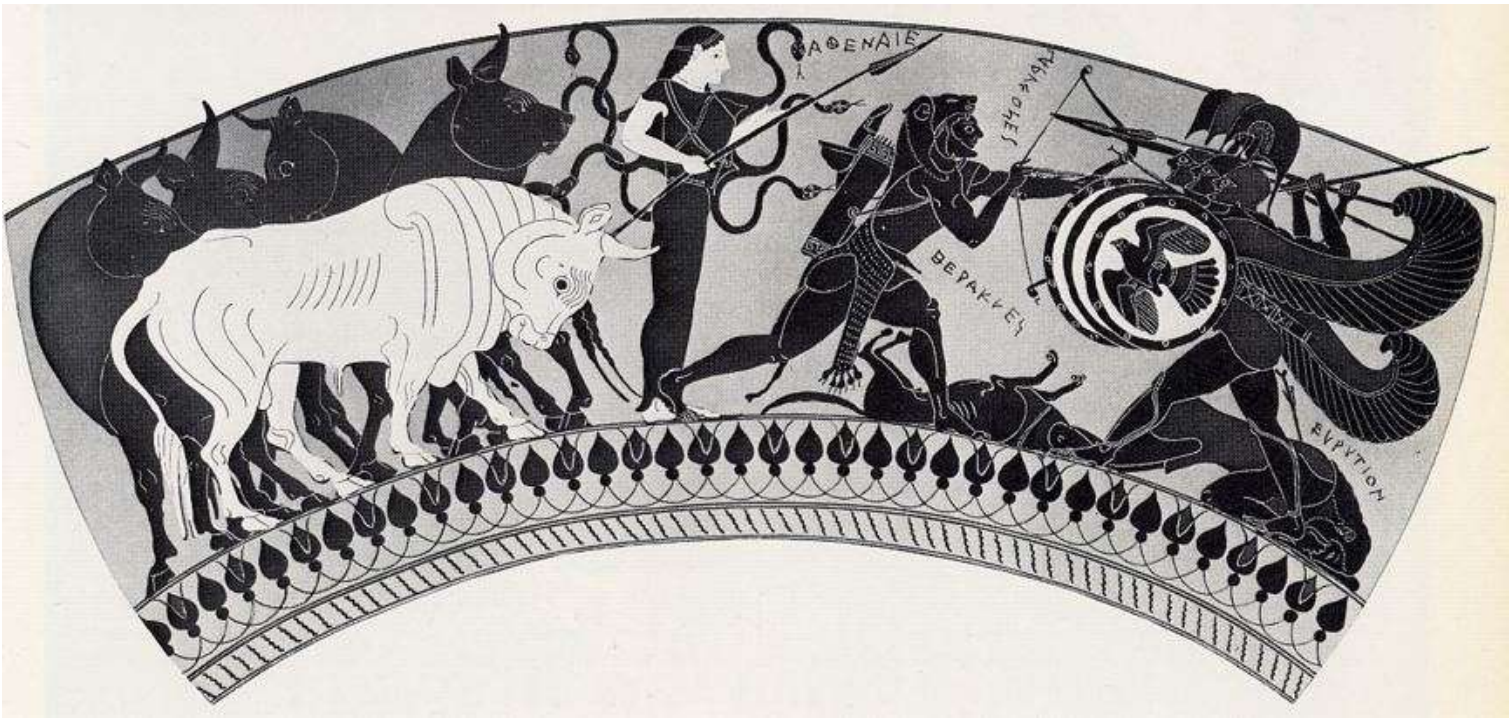
- 200 to 400 mg orally twice daily for 1 week

Then

- 100 to 200 mg orally, daily as an ongoing maintenance dose.



The Three Headed Giant, Geryon, advances to attack Heracles. At his feet lies his two headed dog Orthrus, slain by Heracles, who is seen at the far left, with bow poised, ready to shoot. Reverse side of the above Greek Chalcidian black figure amphora. Southern Italy, c. 540 - 530 B.C, Bibliothèque Nationale de France.



Overview sketch of the Chalcidian black figure amphora; showing Geryon, Hera, the dead Orthrus, and Geryon's Oxen.

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