Amiodarone

**Pharmacology**

Class III antiarrhythmic agent which inhibits adrenergic stimulation (alpha- and beta-blocking properties), affects sodium, potassium, and calcium channels, prolongs the action potential and refractory period in myocardial tissue; decreases AV conduction and sinus node function

**Clinical uses:**

* + Atrial and
  + Ventricular arrhythmias

**Pharmacokinetics**

**1. Absorption**

F = 0.5

* Peak plasma levels in 3 – 7 hours
* Increased rate and extent of absorption when taken with food
* Onset of action may occur in 2 – 3 days or may take up to 3 weeks

**2. Distribution**

* Vd 60 L/kg (extremely large!!!)
* Tissue concentrations are 10 – 400 times plasma levels
* Extensive accumulation in adipose tissue and highly perfused organs (liver, lung, spleen)
* High protein binding (99%)

**3. Metabolism**

Metabolism

* Extensively metabolized in liver and intestinal mucosa
  + Substrate for CYP3A4 and CYP2C8
  + Metabolite – Desethylamiodarone
    - Has sodium and potassium channel blocking activity
  + Inhibits CYP 3A4, 1A1, 1A2, 2B6, 2C9, 2D6
  + Inhibits P-glycoprotein
* Biphasic elimination half-life
* Initial 50% reduction within 2.5 to 10 days
* Terminal elimination ***40 to 60 days (mean 53 days)***

**4. Excretion**

Clearance

* Biliary excretion
* In studies, ranges between 90 and 440 mL/hr/kg
* Not affected by renal function, age, sex

**Dosing guidelines**

Manufacturer Recommendations

IV:

* IV should be administered via a central line
* Concentration 1 to 2.5 mg/mL (can go up to 6mg/mL but ONLY if central line)
* Non-PVC containing bags (use glass bottles)

Loading dose:

* First 24 hours: 150 mg IV bolus (can use 300 mg in certain situations)

Then 1 mg/min x 6 hours

Then 0.5 mg/min x 18 hours if patient does not have oral access can continue 0.5 mg/min and continue until reached **4 – 5 grams total**

PO:

* Loading dose: 800 to 1600 mg daily (in divided doses) until reach **8 – 10 grams total**
* Maintenance dose: 200 – 400 mg daily

|  |
| --- |
| **Question 1:** A is brought into the emergency room by ambulance after passing out. The EMS found the patient in ventricular fibrillation and was given CPR, shocked and administered epinephrine. The ED physician wants to give a bolus and load the patient on amiodarone. What dosing would you recommend? What infusion rate would you recommend to the nurse (amiodarone 900mg/500ml)? |

**Monitoring**

**1. Therapeutic range**

* No established relationship between plasma concentration and effectiveness
* *Not measured in clinical practice*
* In general, want above 1 mg/L but less than 2 mg/L

**Adverse effects**

* Hypo/hyperthyroidism
* Corneal microdeposits
* Hepatitis
* Pulmonary toxicity
* Hypotension (I.V.)
* N/V

**Drug interactions: Not an all-inclusive list**

|  |  |  |  |
| --- | --- | --- | --- |
| **Amiodarone’s effect on other drugs** | **Effect** | **Drug’s affecting amiodarone** | **Effect** |
| Calcineurin inhibitors (Cyclosporine, tacrolimus) | Increase serum concentration | Azole antifungals | Increase QT prolongation |
| Colchicine | Increase concentration/toxicity | Beta-blockers/CCBs (diltiazem/verapamil) | Increase risk of AV block |
| Dabigatran | Increase risk of bleeding |  |  |
| Digoxin | Increase serum concentration | Cimetidine | Decrease amiodarone clearance |
| HMG co-A reductase inhibitors | Increase risk of myopathy | Protease inhibitors | Increase amiodarone toxicity |
| P-glycoprotein substrates & CYP 1A1, 1A2, 2B6 , 2C9, 2D6, 3A4,substrates | Increase concentrations | QT prolonging drugs | Increase QT prolonging effect |
| Tamoxifen | Decrease serum concentration of active metabolite | Any inhibitors or inducers of CYP 3A4 & 2C8 | Increase risk of toxicity |
| mTOR kinase inhibitors (Sirolimus/ everolimus) | Increase serum concentration |  |  |
| Warfarin | Increase INR |  |  |

**Question 2:** **a.** Given the dose that you recommended, how long (days) would it approximately take to fully load a patient with amiodarone IV?

1. Calculate how much amiodarone patient getting on day 1 of load

2. Calculate how much amiodarone patient is receiving on consecutive days

3. Calculate how many days it should take to fully load the patient with loading dose calculated.

**Question 2b:**What if the team decides to convert the patient to oral therapy on the beginning of day #3? How long would it take to load a patient if they are started on 400 mg PO BID?

1. Calculate how much amiodarone the patient received after 2 days.

2. Convert from IV to PO amiodarone.

3. Substract total PO loading dose by the amount the patient has already received after 2 days.

4. Divide the equivalent amount of PO amiodarone the patient already received by the amount the patient will be receiving daily (400mg BID).

**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**