Pharmacological Treatment Of Arrhythmic Tachycardia

Arrhythmia (also called dysrhythmia) effects 2% of the population under the age of 65 and 9% of people above that age (Healthline. 2020). It is caused due to changes of the hearts tissue, activity or through changes in electrical conduction that regulates heartbeat, mainly affecting cardiac rhythm or pumping of the heart (NIH 2020). Stimulants such as increased exertion or stress, blood imbalances, medicines, disease, injury or genetics are all factors that can increase risk of arrhythmia. Effects can fasten, slow or unsteady the hearts natural rhythm. Often there are no distinguishable symptoms of arrhythmia and the condition can go entirely unnoticed by individuals. In some cases, people have reported sensations of irregular heartbeat, as well as faint, dizziness or having difficulty breathing (NIH 2020). An irregular heartbeat may feel like its racing or fluttering. Many heart arrhythmias are harmless. Although they have the potential to be fatal in cases of severe irregularity or in individuals with weak or damaged hearts. Doctors will also recommend treatment if they deem there is probability for the condition to lead to more serious heart problems (Healthline. 2020). Tests like an electrocardiogram (ECG) can be performed for diagnosis of Arrhythmia. Once diagnosis has been confirmed a doctor will prescribe treatment, this can be in the form of drug therapy, placement of a device (eg. Pacemaker), or surgery to repair electrical nerves regulating heartbeat (NIH 2020). If arrhythmia is left untreated there is a possibility that the organ will be at a deficient and not function properly reducing pump ability and blood supply to extremities.

Arrhythmia is simply a deviation of the heart’s natural rhythm. Normal heart rate fluctuates between 60-100bpm (Cleveland Clinic, 2020). The hearts cardiac conduction system causing the pumping action of the heart, is made up of five key elements- Sinoatrial Node (SA); Atrioventricular node (AV); bundle of his; bundle branches and Perkinje fibres. Electrical conduction begins when signals are sent from the SA node. This signal then travels to the AV node affecting left and right atrial area. Signals cause contraction of the hearts muscle wall pushing the blood to the ventricles. The AV node electrical structure consists of two pathways, a slow and a fast pathway. This difference affects the time between atrial contraction and ventricle polarization. This process can be better understood with the inclusion of an ECG illustrating the variation of heart arrhythmias using a waveform. Interference of AV pathways ie disease or injury is the key element of developing increased or decreased heart pumping. The slow AV pathway passes anatomically between the coronary sinus and the tricuspid, it has a longer conduction time, but a short effective refractory period (Cardiac Academy 2020). The fast pathway is located at the start of the interatrial septum. It is the superior route, as it has a faster conduction rate, however a longer effective refractory period (Cardiac Academy 2020). Standard conduction occurs along the fast pathway where the signal then splits and runs down the right and left bundle branches which further progresses to the perkinje fibres distributed around the cardiac ventricles. Arrhythmias increasing cardiac rhythm and heart rate as well as manifestation of premature beats are often misfired through the slow pathway. This demonstrates the process of regular electrical conduction in the heart, following the standardised pathway and velocity.

Tachycardia and Brachycardia are an example of irregular conduction due to fastening or slowing of the heart’s rhythm. Brachycardia is a decrease in heart rhythm (less than 60bpms at rest). Trained athletes typically have very low HR’s to begin with and if symptoms of disease

aren’t present such as weakness, fatigue, dizziness, fainting, chest discomfort, palpitations, or respiratory distress then disease presence is not considered clinically significant (BC campus, 2020). In some cases, athletes can have a resting heart rate as low as 40bpm. Reports of light-headedness is a clinically important indicator for presence of Brachycardia illness. The body feels faint due to the heart not pumping enough blood to meet the bodies need. This causes you to feel lightheaded or faint due to dysfunction of the heart conduction system specifically the SA or the AV node reducing cardiac action potential meaning less heart contraction and less oxygen rich blood being pumped from the left ventricle to the head and extremities (Myheart, 2020). An ECG will likely confirm or reject this diagnosis. Drug effects target SA and AV node, stimulating normal conduction velocity, stabilizing heart rate.

Tachycardia is the function of increased or irregularly fast heartbeat, ie higher than 100bpms at rest. Tachycardia, specifically atrial tachycardia or atrial fibrillation is the most common type of arrhythmia. In a 2013 study, the worldwide estimated number of individuals with Atrial fibrillation conditions in 2010 was 33.5million (Healthline. 2020). Atrial fibrillation produces an abnormal or enhanced automaticity. This happens due to the hearts cell membrane becoming more permeable to sodium causing conduction systems to go into overdrive and quicken electrical firing and heart contractility. Antiarrhythmic drugs function primarily to block or inhibit channel/receptors of the heart promoting arrhythmia. Once drug targets have made effect, the body will naturally recover and produce normal rhythm. This process occurs almost instantly through IV administration.

Vaughn Williams classification of antiarrhythmic drugs categorizes them into four classes based on their dominant mechanism of action.

1. Class I drugs work by blocking sodium channels. This decreases the rate of depolarization and slows conduction velocity (delays phase 1 effective refractory period)
    1. IA- moderately depress depolarization
    2. IB- weak effect on depolarization
2. Class II drugs act on Beta 1 receptors preventing the action of catecholamines on the heart. Depress sinus node automaticity and slow conduction through AV node which results in decreased rate and contractility.
3. Class III drugs block potassium channels that are responsible for repolarization. This leads to increase in duration of action potential and increased effective refractory period. Class III drug agents- bretylium, amiodarone, ibutilide, sotalol, dofetilide, vernakalant and dronedarone.
4. Class IV calcium channel blockers. Depress calcium-dependent action potentials. Reduce heart rate and conduction. Act particularly on SA node and AV node.

Current evidence favours Class III drugs, potassium channel blockers in treatment of Tachycardia and increased heart rate. In cases of life and death one drug by the name of Amiodarone is used due to its expansive amount of target potentials. In most countries Amiodarone is one of the most effective and commonly prescribed antiarrhythmics on the market apart from other drugs such as digoxin, and beta blockers (NPS, 2010). Besides being a potassium channel blocker, Amiodarone also has the ability to block sodium channels, calcium channels, and even some alpha and beta receptors. This works to prolong the phase 3 action potential of cardiac cells during refractory period (ESC, 2020). Despite this drug having the combined target potential of all four drug classes affecting all ion channels and receptors of the cardiac conduction system, it is not a miracle drug. Amiodarone does have ample drug effect

including systematic effect of modest reduction in patients with high risk of sudden cardiac death (reduction of 20-30%). Amiodarone cannot treat all forms of arrhythmia (only tachycardia and fibrillation) as well as it is misadvised for use on minor rhythm disturbances due to the drugs toxicity. It is not recommended for individuals with indicators of bradycardia and low heart rate, as it can worsen the already pre-existing condition and become fatal. Ailments that can be treated with amiodarone range from recurrent atrial fibrillation, patients at intermediate risk of arrhythmic death, as well as patients suffering from post-myocardial infarction and heart failure (NPS,2010). Treatment solutions aren't always required for acute symptoms of atrial fibrillation and if needed treatment can be provided in the form of oral medication of amiodarone. Intravenous therapy isn't required and would be unnecessary increase of toxins in the body.

Amiodarone has a standard daily maintenance dose of 200mg in oral form. In this dose of that there is 75mg of iodine in the drug. This is way above our normal daily iodine requirement that being between 0.2 to 0.8mg. Amiodarone delivers more than one hundred times the necessary amount of iodine to the body daily (NPS,2010). This is one example of the drugs severe toxic nature and explains how this drug can produce such a large array of side effects, which in some cases is disproportionate to its treatment effect. Amiodarone isn't always the best drug solution. It is reported that adverse side effects have been shown to develop in 15-50% of patients following administration of drug in the first year and that figure increases over time with prolonged drug administration. Some of the side effects of Amiodarone include pulmonary fibrosis, blue-grey skin discolouration, neuropathy, hepatoxicity, corneal microdeposits, and because of its iodine content can cause hypo-hyper thyroid dysfunction. Long half-life (estimated 30-180 days) the drug continues to linger in patients' tissues for months after discontinuation of drug therapy. Due to the fact, following prolonged drug therapy of Amiodarone GP's will recommend semi-annual testing such as thyroid hormone transaminase tests, chest x-ray as well as an ECG from amiodarone patients to ensure drug toxicity isn't overly effecting body systems (NPS, 2010).

Absorption and bioavailability of amiodarone is very slow and sometimes variable (bioavailability normally around 30%) and can take weeks for therapeutics effects to appear. Latency can be reduced through high-loading oral administration over IV (ESC,2020). Intravenous administration of Amiodarone isn't recommended due to its potential for developing of acute hypotensive symptoms, as well as being damaging to veins. If required IV Amiodarone is administered through a central line at 300mg induced over a period of 20 minutes to two hours, followed by a further 900mg over a 24hr period (NPS,2010).

Australian pharmaceutical company Ipsen PTY, released a new antiarrhythmic drug "heart-a-settle" as a potential pharmaceutical treatment for tachycardia with significant drug target properties similar to Amiodarone, but with less adverse side effects. Heart-a-settle fits in Vaughn's William classification of drugs III group as the drug performs as a potassium channel blocker. Heart-a-settle is intentioned in treatment of tachycardia, in which it affects the body by decreasing heart rate to normal rhythm with fewer side effects than pre-existing marketed drugs. This drug is purposed to function as a superior treatment solution than Amiodarone in prolonged drug therapy. Although, Amiodarone is still recommended in incidences where patients have high risk of sudden cardiac death or life-threatening arrhythmia due to the drug's efficacy in fatal disease circumstance. In comparison, heart-a-settle is a lot less toxic, with lesser concentrations of harmful chemicals alike iodine. Clinical testing is yet to occur in comparison of drug performance among drug 1 heart-a-settle intervention drug and drug 2 Amiodarone which is our control. Testing will be held following a randomised control trial where both participants

and patients will be blind to drug groups. Group selection will occur through randomization of patients assigned to different drug groups through block randomised selection. This technique being random allocation of group participants of a clinical trial into equally proportioned treatment samples. Random selection will be implemented in my trial to eliminate bias among testing and produce more accurate data. Within the trial drug doses will be as recommended for patient situation however regular daily maintenance doses are 100mg/kg of Heart-a-settle and 200mg/kg of Amiodarone. Testing of drug comparisons will be made routinely throughout the duration of the trial among both intervention groups in development of drug findings. Research methods will include, analysis of heart condition with regular screening of ECG, cardiac echo, holter monitor, as well the addition of a tissue organ bath. We hypothesize that the data will show Heart-a-settle to be less harmful to patients than Amiodarone with a protective effect on structure and mechanical properties of the aorta in arrhythmic patients through decreased toxic chemical concentration. In comparison, heart-a-settle is administered at half the dose ratio compared to Amiodarone, this effects duration of drug administration as drug has a slower releasing bioavailability which in return extends therapy period. Patients administered with amiodarone should have faster therapeutic effects than the alternative heart-a-settle but with the downside of increased toxicity, side effects and long half-life. Good clinical response may be observed in patients receiving amiodarone even after discontinuation of drug administration due to long half-life and inducibility. Lesser toxins in heart-a-settle will mean drug is metabolized in the body at a faster rate and excreted from body's systems in a lot shorter time (couple weeks > couple months).

Organ bath tests will examine efficacy and potency of drug solutions on cardiac tissue. In this experiment, trial conditions will follow administration of drug solution on tissue with resting BPM of 90. We theorize that amiodarone will have faster efficacy of desired results, than heart-a-settle. Furthermore, another experiment will be conducted testing the drug solutions of acute tachycardia. Amiodarone is not recommended in acute incidences due to its drug potency potentially having lethal effects, resulting in heart block or severe bradycardia. Heart-a-settle should still have some decreased arrhythmic affect due to misuse of drug in improper conditions, however, will be a lot less.

In conclusion, Amiodarone is a useful drug therapy for treatment of arrhythmic tachycardia. Especially in incidences of high risk sudden cardiac death due to extreme drug potency. Our new drug heart-a-settle is a lot less harmful due to daily maintenance dose ratio being half that of Amiodarone as well as a total reduced volume of toxic chemicals in new drug solution. Dependent effects of heart-a-settle produce clinically significant outcomes as its predicted effectiveness as a derivative of Amiodarone for prolonged use as tachycardia treatment. Follows reduced morbidity due to half-life of drug and side effects. These projected results should be easily reproduced in a clinical trial and organ bath solution further implementing the effectiveness of the new drug therapy, heart-a-settle.