Rate vs rhythm: beta blockers and antiarrhythmics as pharmacological options for the treatment of postoperative atrial fibrillation

Abstract

Post-operative atrial fibrillation (POAF) is one of the most recognised complications of cardiac surgery. Although its exact pathophysiology remains unknown, evidence suggests it is multifactorial and that it directly affects patient outcomes post cardiac surgery. It is associated with not only an increased risk of heart failure, renal failure and stroke but also mortality. Pharmacological agents such as beta blockers and antiarrhythmic drugs are well established and extensively used for both the prevention and treatment of post-operative atrial fibrillation. This article will explore the pharmacological treatment of post-operative atrial fibrillation with specific reference to metoprolol and amiodarone and the pharmacokinetic and pharmacodynamic effects of both drugs. It will briefly discuss the evidence reviewed on the effectiveness of these drugs on POAF and on the recommendations from the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery on how post-operative Atrial fibrillation should be treated.

Key words

post-operative atrial fibrillation (POAF), beta blocker, amiodarone, antiarrhythmic, metoprolol, normal sinus rhythm (SR)

Key points

This article presents a critical discussion of the pharmacotherapeutic treatment of post cardiac surgery atrial fibrillation.

It will discuss the pathophysiology of the heart both in normal sinus rhythm (SR) and in post-operative atrial fibrillation (POAF).

Treatment of POAF trends towards either rate control or rhythm control with beta blockers or antiarrhythmics drugs as main choice of treatment (Kirchoff 2016).

For the purpose of this discussion the two drugs of choice are metoprolol, a common beta blocker and amiodarone, an antiarrhythmic drug.

Both drugs are well established in the treatment of POAF which is a common occurrence within the context of cardiac surgery.

The discussion will focus on the pharmacodynamic and pharmacokinetic effects of metoprolol and amiodarone in relation to the prevention and treatment of POAF.

Introduction

Atrial fibrillation (AF) has been recognised as one of the most prevalent arrhythmias worldwide (National Institute of Clinical Excellence (NICE) 2014). It is an arrhythmia, identified by uncoordinated atrial activation, that results in the deterioration of the mechanical function of the heart (Mostafa et al. 2012). It has been described by Darbar (2016) as being a disease with global epidemic proportions. The prevalence of AF is predicted to increase in the future due to an increasingly aged population, with its occurrence approximately doubling with each decade of age. This is a view voiced by many including Eftekhari (2020) and Norhayati et al. (2020) who go further and relay the significant repercussions this will have on cardiac mortality and morbidity rates. AF is one of the most recognised complications of cardiac surgery with Piccini et al. (2013) and Raiten et al (2015) both indicating an incidence of up to 40% of patients following coronary artery bypass surgery (CABG) and 64% with accompanying valve surgery. Post-operative atrial fibrillation (POAF) often presents within forty-eight hours but can occur up to six days after surgery. The 2020 ESC guidelines for the diagnosis and management of AF state that POAF is associated with an increased risk of renal failure, stroke and mortality (Piccini et al. 2013, Raiten et al. 2015 and Hindricks et al. 2020). Mostfa et al. (2012) found that AF following pharmacological cardioversion can reoccur up to six months after the initial post-operative episode suggesting POAF can be paroxysmal. It is important when examining POAF and its treatment that there is an understanding of what is normal within heart function.

The exact pathophysiology of POAF remains unknown, however authors such as Kappenbergger (2013) and Musa et al. (2018) agree that evidence suggests it is multifactorial. Although often a transient condition that does occasionally resolve spontaneously, POAF has been described as a malignant condition which can directly affect

patient outcomes post cardiac surgery (Attaran et al. 2012, Raiten et al. 2015 and Gillinov et al. 2016). In essence, the development of POAF is due to ectopic firing or a re-entry mechanism which may have been initiated by the inflammatory response caused by the surgery or by the presence of an atrial substrate (Younis 2017 & Norhayati et al. 2020). POAF can be influenced by a number of factors such as a patient's underlying condition or by events that may have occurred intra-operatively or post-operatively. Mostafa et al. (2012) and Raiten et al. (2015) both describe surgical injury to the right atrium, atrial ischaemia, atrial stretch, pulmonary vein manipulation, metabolic disturbances and cardiopulmonary bypass (CPB) as events which can influence the development of POAF. Mostafa et al. (2012) believe it is worth noting that there is conflicting evidence over whether or not CPB increases the risk of POAF (Asher at al. 1998, Abdelhadi et al. 2004 and Lamm et al. 2006 as cited by Mostafa et al. 2012). Interestingly the Atrial fibrillation suppression trial II (AFIST II) carried out by White et al. (2003) and cited by Mostafa et al. (2012) found a higher prevalence of POAF in patients who received a large amount of fluid post-operatively suggesting atrial hypervolaemia as a risk factor for POAF. Schotten et al. (2011) also established atrial pressure and volume overload to be predictors of an increased risk for POAF. Despite the research conducted over the years on the risk and causes of POAF, Norhayati et al. (2020) highlight the lack of definite strategies for preventing POAF.

Pharmacotherapy in POAF

Pharmacological agents such as beta blockers and antiarrhythmic drugs (Figure 1) have been used extensively as prophylaxis and as treatments for POAF. Both types of drugs are well-established treatments, but it is how they influence the electrical activity of the heart that determines the category they fall into within the Vaugh Williams classification (Eftekhari

2020). Although there are five classifications this discussion will focus on selected drugs from class II and III because they represent the drugs which are most commonly used in the cardiac surgical intensive care unit.

DRUGS	COMMON SIDE-EFFECTS	CONTRAINDICATIONS	EXAMPLES OF DRUG INTERACTIONS
Amiodarone	Arrhythmias; hepatic disorders; hyperthyroidism; nausea, respiratory disorders; skin reactions	Avoid in severe conduction disturbances & sinus node disease (unless pacemaker insitu); iodine sensitivity; thyroid dysfunction; sino-atrial heartblock & sinus bradycardia (except in cardiac arrest)	Histamine H1 anagonists- eg. Loratadine. Histamine H2 anagonists- eg. Cimetidine. Antidepressants- eg. Citalopram. Immunosuppressants- eg. Cyclosproine. HMG-CoA reductase inhibitors- eg. Simvastatin. Cardiovasculars- eg. Cardiac gyycoside-digoxin. Antiarrhythmics- eg. Procainamide, Flecamide. Antihypertensives- eg. Beta blockers and calcium channel antagonists. Anticoagulants- eg. Warfarin. Antibiotics-eg. Fluorooquinolones & macrolides.. Other substances- eg. Grapefruit juice
DRUGS	COMMON SIDE-EFFECTS	CONTRAINDICATIONS	EXAMPLES OF DRUG INTERACTIONS
Metoprolol tartrate	Abdominal discomfort; bradycardia; confusion; depression ; dizziness ; GI disturbances; dyspoea; fatique; headache; peripheral coldness; rash; sleep disturbances; syncope; heart failure; paraesthesia; palpitations; postural disorders.	Asthma; cardiogenic shock; hypotension; bradycardia; Prinzmetal's angina; second & third degree heart block, sick sinus syndrome; uncontrolled heart failure; severe peripheral vascular disease. History of bronchospasm and COPD.	Calcium antagonists- eg. Verapamil. Antiarrhymics- eg. Amiodarone. Cardiovascular- eg. Digoxin. Oral antidiabetics &Insulin. Antidepressants- eg. Fluoxetine. Centrally acting antihypertensives- eg. Clonidine. Alpha blockers- eg. Doxazosin. NSAIDS. Other substances- eg. Alcohol.

Figure 1: Overview of amiodarone and metoprolol (Source: BNF 82/Drugs.com/medicines.org.uk, accessed Aug 2022)

Beta-blockers

Beta blockers have been described as one of the oldest classes of cardiovascular drugs and are the most frequently used in the treatment of arrhythmias such as AF among other cardiovascular diseases (Poirer et al. 2013). They affect the SAN and AVN by blocking beta receptors through competitive inhibition, which results in a decrease in sympathetic tone thereby reducing adrenergic activity (Neal 2016 & Eftekhari 2020). The consequences of

which slows the force and rate of heart contraction, hence reducing the demand for oxygen in myocardial tissue. Although described by Dorian and Angaran (2013) as being potent drugs, they are a safe and effective way of treating symptomatic patients by rapidly controlling ventricular rate. Agesen et al. (2019) concur but warn against making an assumption of a class effect. They emphasise the importance of recognising that beta blockers have different attributes and that their clinical indications, side effects and contraindications will differ according to specific attributes. Poirer et al. (2013) and Wagner et al. (2020) both described how beta blocker specificity refers to the affinity the drug has for one type of receptor over another and therefore the specificity for cardiac effects. First generation beta blockers display a non-selective affinity and block both beta 1 and 2 receptors, whereas second generation are cardio selective (but not cardio specific) and provide selective blockade for beta 1 receptors but have less of an effect on beta 2 receptors. Third generation beta blockers are beta1 receptor selective and exhibit vasodilatory properties (Poirer et al. 2013, Hocht et al. 2016). They all differ in respect to half-life, protein binding, distribution and elimination route as well as differences in duration and interactions (Berger et al. 2018). Due to the presence of beta 1 and 2 receptors in other locations of the body (significantly in the respiratory system), careful consideration must be made when prescribing a beta blocker for POAF as to how its efficacy will be affected by a patient's co-morbidities in relation to these differences.

Metoprolol is a class II cardio selective beta blocker which was developed in the 1960s. Although used for the treatment of arrhythmias, Morris and Dunham (2020) outline its use in the treatment of hypertension and myocardial infarction. In arrhythmias such as AF, metoprolol works by prolonging the refractory period at the AVN (www.Drugbank.com). The antiarrhythmic effect of beta blockers is associated with their capacity to impede beta receptor mediated adrenergic neural activation (Ladage et al. 2013). Post cardiac surgery

patients tend to experience a significant catecholamine surge and beta blockers, such as metoprolol, will exert an antagonistic effect on chronotropic and inotropic pathways which will lessen the effects of this surge (Mukherrjee 2020). Mukherrjee (2020) describes how this temporary blockade will reduce the frequency at which myocytes are triggered to initiate electrical impulses. This has the benefit of reducing the activity of the heart and the ventricular rate which consequentially will improve diastolic filling time, improve perfusion and reduce oxygen requirements. This in turn will reduce associated AF symptoms of palpitations, tachycardia and shortness of breath (Poirer et al. 2014). Metoprolol's inhibitory action on the SAN, AVN and myocardial contractility also has the potential to cause adverse effects such as hypotension, bradycardia and in some cases can cause dyspnoea due blockade of beta-2 receptors in the lungs. Although considered cardio selective in relation to the inhibition of beta 1 receptors, metoprolol does also exhibit some inhibiting effects on beta 2 receptors but to a lesser extent and only at higher doses (Frishman 2013).

The pharmacokinetic factors of absorption, distribution, metabolism and excretion are all important in the clinical response of a drug (Angaran 2013). Metoprolol is well absorbed in the gastrointestinal tract and the bioavailability for the route is 40-50% depending on oral formulation administered. This increases to approximately 70% when taken with food. As with intravenous forms of all drugs, the bioavailability of this route is 100%. Metoprolol is a lipophilic drug which has the ability to cross the blood brain barrier with a cerebrospinal fluid concentration that is close to that found in plasma (Frishman 2013, Hocht et al. 2016). Its molecules are not highly bound to the proteins found in plasma and only a small percentage, approximately 10%, are bound to serum albumin (Ladage et al. 2013). Metoprolol goes through an extensive first pass hepatic metabolism which is primarily driven by the enzyme CYP2D6 and CYP3A4 to a lesser extent and is dependent on oxidation phenotype (Ladage et al. 2013, Berger et al. 2018). This results in wider variations in plasma concentration, a

shorter half-life and because of this hepatic metabolism metoprolol is more susceptible to drug interactions (Poirer et al. 2014, Dunham et al. 2020). It has a half-life of three to four hours which can increase to seven to eight hours in the elderly due to age related changes in pharmacokinetics (Jansen et al. 2012). Lipophilic drugs such as metoprolol have a low water solubility thereby, due to changes in body composition in the elderly, volume of distribution will increase causing the prolongation of the drugs half-life (Jansen et al. 2012). Elimination of metoprolol is via the kidneys. In patients with normal kidney function the amount excreted as unchanged drug is approximately 5-10 % depending on the formulation administered. There is no evidence to suggest that dose adjustment is required with renal impairment but in patients with hepatic impairment titration up should be done with caution (Morris & Dunham 2020). When prescribing beta blockers it is important to take into consideration the possibility of factors such as ethnicity, sex, obesity, polypharmacy and age having the potential to alter the pharmacokinetics of the drug (Agesen et al. 2019). Dunham et al. (2020) highlighted an important fact that many of the studies on the pharmacokinetics and pharmacodynamics of beta blockers were carried out on young to middle aged patients rather than older patients who, due to the aging population, tend to be the main recipients of the drug. This may well have consequences as any study results may cause the pharmacokinetic differences and therefore bioavailability in the elderly to be underestimated.

Anti-arrhythmic drugs

Although rate control in the form of beta blockers is recommended as the first line of treatment for AF, the results of a study by Bruggmann et al. (2020) suggested that amiodarone, an anti-arrhythmic drug, was still most commonly used as the initial treatment for POAF management. Amiodarone is a class III anti-arrhythmic drug, however its unique

pharmacodynamics have been found to potentiate effects through all Vaugh Williams antiarrhythmic classes ((Efktehari 2020, Srinivasan et al. 2019). Amiodarone acts by affecting the conduction and refractory periods in the myocardium, and hence it relaxes the smooth muscle that lines the wall of the blood vessel (Neal 2016, Biancatelli et al. 2019 and Efterkhari 2020). In addition to electrophysiological properties amiodarone, when administered intravenously, will also have an effect on the haemodynamics of a patient. It has been deemed safe for use in patients with heart failure and those with structural disease due to it low risk of proarrhythmia and lack of negative inotropy(Hindricks et al. 2020).

Amiodarone has a wide variability in bioavailability, averaging 30-80% after oral administration as absorption is incomplete and slow (Mackenzie et al. 2011). Its onset of action is not immediate and can take up to a number of weeks to reach therapeutic levels (Biancatelli et al. 2019). Bioavailability can be influenced by impaired liver function, age related biological changes and drug interactions. Amiodarone is hepatically metabolised by CYP3A4 and CYP2C8 enzymes and eliminated primarily through biliary excretion in the gastrointestinal tract. A small amount of the metabolite Desethyl-amiodarone (DEA) is excreted in the urine (Biancatelli et al. 2019, Vyskocilova et al. 2017). Due to its lipophilic properties, it has a high but variable volume of distribution and it accumulates mainly in adipose tissue and highly vascular organs such as the liver and lungs. (Loewe et al. 2014, Vyskocilova et al. 2017). With a half-life of up to 100 days its actions persist even after it has been discontinued (Biancatelli et al. 2019).

Amiodarone is mainly bound to albumin proteins and to a much smaller extent beta-lipoprotein and alpha-1 acid glycoprotein. It influences CYP-enzyme and P-glycoprotein activity which consequentially results in the alteration of concentrations of drugs that are metabolised by these pathways (Vyskoliova et al. 2017, Biancatelli et al. 2019). These alterations lead to adverse reactions occurring when the drug interacts with amiodarone

(Mackenzie et al. 2011). For example, Vyskoliova et al. (2017) discuss the signification of the interaction between amiodarone and metoprolol. Administration of an amiodarone loading dose will cause the plasma concentration of metoprolol to double which increases the potency of the metoprolol giving way to an increased risk of bradycardia and proarrhythmia.

Although highly effective in treating arrhythmias amiodarone, both in oral and intravenous formulation, is known to cause a wide range of both cardiac and extracardiac adverse effects (Bruggman et al. 2020). For example, bradycardia occurs due to reduced function at the SA node. Despite being considered to have a smaller risk of proarrhythmia than other antiarrhythmic drugs, when combined with other commonly prescribed drugs, such as beta and calcium channel blockers, the additive effects can result in prolonged QT interval and subsequent proarrhythmias (Mackenzie et al 2011, Vyskocilova et al. 2017, Biancatelli et al. 2019). Amiodarone when given intravenously has an increased risk of causing infusion related hypotension. It has been suggested that infusion related hypotension may be partly due to the excipient polysorbate 80, which has vasodilatory properties, rather than amiodarone itself (Vyskocilova et al. 2017). In addition to these, extended use and higher maintenance doses of amiodarone may predispose patients to potential liver, thyroid and pulmonary toxicity (Mackenzie et al. 2011). Despite how effective amiodarone is in treating AF, Bruggman et al. (2020) recommend only using it for short periods due to its toxicity. Although the ESC 2020 guidelines for the management of AF also recommend that amiodarone is used as a second line treatment due to its extracardiac adverse effects (Hindricks et al. 2020) Bruggman et al. (2020) found that, despite these recommendations, amiodarone was still the most commonly used treatment for POAF.

Conclusion

Pharmacological conversion continues to be the primary choice for treating POAF with both amiodarone and metoprolol being well established treatments (Kirchoff et al. 2016). As previously discussed, despite numerous studies being conducted into the efficacy of both drugs, there is still no clear indication over which is more effective (Gillinov et al. 2016). That being said, evidence available has led to the European Society of Cardiology (ESC) and the European Association for Cardio-thoracic Surgery (EACTS) recommending that rate control in the form of beta blockers should be the first line of treatment in haemodynamically stable patients. Amiodarone, due to its extracardiac adverse effects should only be used in patients that are haemodynamically compromised or in those that beta blocker therapy is contraindicated. With research currently being undertaken in the direction of pharmacogenetics, future treatment may well be tailored to the individual patient, especially those with pre-operative risk factors for AF. For now, treatment will continue to be based on guidance from the ESC and EACTS published recommendations.

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