Beta blocker use in cardiovascular disease

Introduction

Beta blockers have a long and well-established history of use for a variety of indications, and are one of the most widely used pharmacological agents for patients with cardiovascular disease. Most beta blockers can be used safely in adult patients and there is a sound evidence base for their efficacy in conditions such as angina, atrial fibrillation, heart failure and myocardial infarction.

Due to their frequency of use, it is important that practitioners have a comprehensive understanding of the mechanism of action of beta blockers as well as their role in therapy. Although beta blockers may be used in the treatment of a range of different pathological conditions, this article will focus on their use in cardiovascular disease in particular. The pharmacology of beta blockers will be described, along with a summary of the evidence for their current place in therapy and important practical considerations for their use.

Beta adrenergic receptors

The primary control system associated with the regulation of heart rate, digestion, respiratory rate, pupillary response and urination is the autonomic nervous system (ANS). The sympathetic nervous system (SNS) is one of the divisions of the ANS and is mainly associated with stimulating 'fight or flight' responses such as increasing heart rate and slowing digestion. These responses are mediated by the release of endogenous catacholamines such as adrenaline (epinephrine) and noradrenaline (norepinephrine). Adrenaline and noradrenaline are synthesised and released in the adrenal medulla in response to sympathetic stimulation and act as neurotransmitters in the SNS, binding to adrenoreceptors in order to exert their action. Unlike adrenaline, noradrenaline is also synthesised and released in the postganglionic nerve endings and acts as the main neurotransmitter in the SNS (Figure 1).
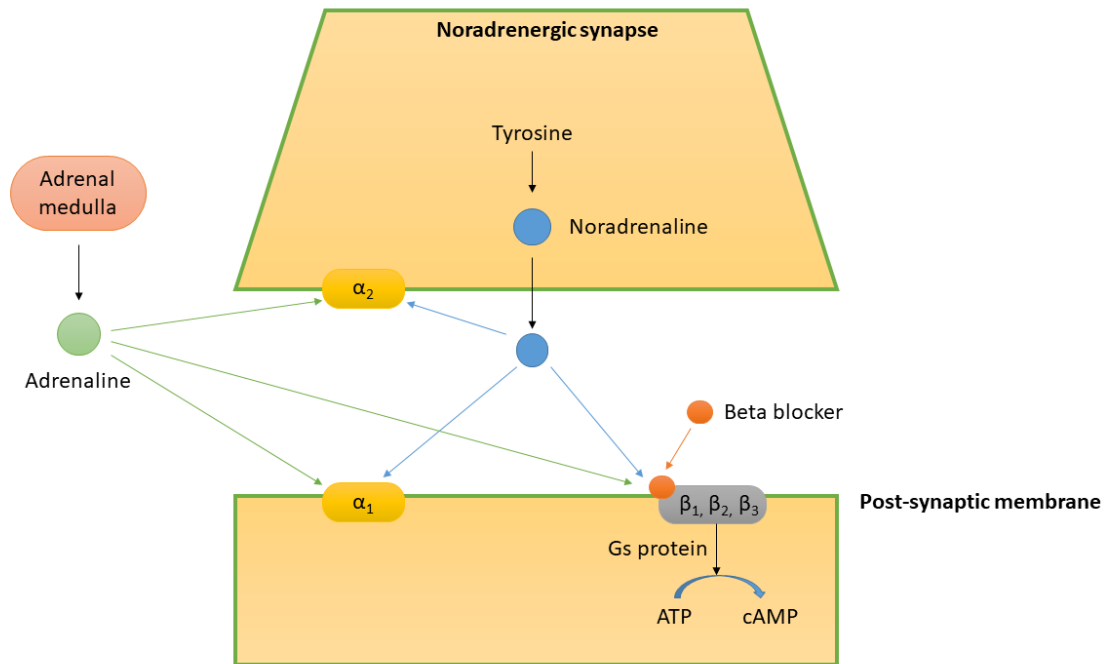
Figure 1: Catecholamine release and binding of adrenergic receptors in the sympathetic nervous system. Beta blockers act on beta receptors to inhibit the action of noradrenaline and adrenaline.

Adrenoreceptors are present in a variety of tissues, and are divided into two main groups: α (alpha) and β (beta), with further subtypes (α_1, α_2, β_1, β_2, β_3) that show different affinities to binding adrenaline and noradrenaline. The physiological action of adrenaline and noradrenaline depend on the subtype and location of the adrenoreceptors that they bind to (see Table 1).

Adrenoreceptors are a major target of drug action; the selective stimulation and blockade of various adrenoreceptor subtypes is responsible for a significant area of therapeutics (Rang et al. 2016). Understanding the action of adrenaline and noradrenaline on beta adrenoreceptors in the heart and vasculature can aid appreciation of the role of beta blockers in the treatment of cardiovascular disease.

Beta receptors in the heart

Beta receptors, mainly of the β_1 subtype, are located on the myocardium as well as nodal tissue and the conducting system (López-Sendón et al. 2004). Beta receptors are Gs-protein coupled receptors, which when activated by catecholamine binding, stimulate the formation of cAMP from ATP (via adenylyl cyclase activation) (Daaka et al. 1998). Intracellular cAMP activates protein kinase A (PKA), which phosphorylates the membrane calcium channel responsible for calcium entry into the cell. PKA also enhances calcium release from the sarcoplasmic reticulum. Increased cAMP therefore causes a subsequent increase in myocyte contractility, conduction velocity and heart rate (Lemoine et al. 1988).

Inhibition of this process can be achieved by the use of beta blockers, which bind to the receptor either at the ligand binding site (competitive antagonism), or at another site on the receptor that, upon binding, will change the receptor structure and render it inactive (non-competitive antagonism). In the heart, beta blockers will therefore cause a decrease in contractility, conduction velocity, heart rate and relaxation rate (Waller and Sampson 2017).

Beta receptors in blood vessels

Vascular smooth muscle contains β_2 receptors that have a high affinity for binding circulating adrenaline (compared with noradrenaline released by sympathetic nerve endings). When these receptors bind adrenaline, the increase in cAMP leads to an inhibition of myosin light chain kinase (which usually phosphorylates smooth muscle myosin), resulting in smooth muscle relaxation (Tanaka et al. 2005). Although β_2 receptors only have a slight impact on basal vascular tone, beta blockers will cause a small degree of vasoconstriction by blocking cAMP-mediated vasodilation that usually opposes more dominant vasoconstrictor influences (e.g. alpha-receptor effects).

Beta blocker properties

The indiscriminate blockade of both β_1 and β_2 receptor subtypes is seen with first generation, 'nonselective' beta blockers (e.g. propranolol); 'cardioselective' beta blockers (e.g. bisoprolol, atenolol, metoprolol) are those that show greater affinity to the β_1 subtype mainly found in the heart. The cardioselectivity of these beta blockers is dose-dependant, with progressively more β_2 blockade occurring at higher doses (McDevitt 1987b). Third generation beta blockers (e.g. carvedilol, nebivolol) have additional vasodilatory activity via alpha-adrenoreceptor (α_1) blockade and production of endothelial nitric oxide synthesis, but with varying cardioselectivity (Bristow 2000; Kalinowski et al. 2003).

Beta blockers that are lipophilic (e.g. propranolol, metoprolol) are able to penetrate the blood-brain barrier to elicit effects on the adrenergic nerves in the central nervous system. As such, central side-effects such as sleep disturbance, fatigue, hallucinations and vivid dreams are more likely to be seen with these beta blockers. Lipophilic beta blockers are well absorbed from the gut but undergo extensive first-pass metabolism in the liver (McDevitt 1987a).

Hydophilic beta blockers (e.g. atenolol), by contrast, are incompletely absorbed from the gut but do not undergo hepatic metabolism, and have longer half-lives than lipophilic beta blockers. Dosing is therefore usually only needed once daily with hydrophilic beta blockers, whereas lipophilic beta blockers have shorter half-lives and may require multiple daily dosing.

Beta blocker mechanism of action and role in therapeutics

Beta blockers currently feature in the treatment of angina, myocardial infarction, atrial fibrillation, heart failure and hypertension. Their mechanism of action in these conditions is outlined below, along with their role in therapy.

Angina

The pathophysiology of angina involves reversible myocardial ischaemia as a result of coronary artery disease, where myocardial oxygen supply cannot meet demand on exertion. Consequentially, anaerobic metabolism may result in the pain of angina pectoris, as well as shortness of breath. In order to help redress this imbalance, beta blockers may be used to both help reduce myocardial oxygen demand and improve supply (Waller and Sampson 2017).

Myocardial oxygen demand is reduced by the action of beta blockers decreasing the force of cardiac contraction (negative ionotropy). By antagonising the β_1 receptor, beta blockers inhibit the stimulation of intracellular cAMP, causing a decrease in calcium loading and subsequent contractile force.

A decrease in heart rate (negative chronotropy) also contributes to a reduction in myocardial oxygen demand. The spontaneous beating of the heart is controlled by the I_f current in the sinoatrial node, which is regulated by the SNS via intracellular cAMP. Beta blockers inhibit this pacemaker current by inhibiting cAMP production, so that the I_f channel requires a more negative intracellular voltage in order to be activated (Difrancesco 2010). The resulting slower heart rate lengthens diastole, allowing more time for coronary perfusion, thereby increasing oxygen supply. The combination of a reduced chronotopy and ionotropy also results in a decreased cardiac output and lower blood pressure, further decreasing myocardial oxygen demand and cardiac work.

Beta blockers can be a useful prophylactic antianginal drug for patients with stable angina pectoris, and can reduce ischaemic events after presentation in those with unstable angina. Although evidence suggests that beta blockers do not have a significantly positive or negative impact on mortality (Huang and Fox 2012), various studies demonstrate their benefits in controlling exercise-induced angina, improving exercise capacity and limiting both symptomatic as well as asymptomatic ischaemic episodes (Gibbons et al. 2003; Montalescot et al. 2013).

As such, beta blockers are one of the first-line agents for the treatment of angina (Table 2).

Myocardial infarction

Beta blockers used post-myocardial infarction (MI) (where occlusion of coronary arteries results in irreversible myocardial ischaemia, with or without ST-elevation) can reduce oxygen demand (due to reduced heart rate, blood pressure and contractility) and relieve ischaemic chest pain as described above.

Beta blockers have had a longstanding role in the treatment of MI (both acute treatment and in secondary prevention) following evidence that their use reduces all-cause mortality, sudden death, cardiac mortality, morbidity and re-infarction (Freemantle et al. 1999; Dargie 2001; Fauchier et al. 2007). In the early stages they can decrease infarct size, and increase the ventricular fibrillation threshold post-MI, reducing the risk of ventricular fibrillation and sudden cardiac death (Nuttall et al. 2000; López-Sendón et al. 2004).

In secondary prevention, their mechanism of action is unclear, but may involve reducing subsequent pathological cardiac remodelling (e.g. ventricular hypertrophy, ventricular dilation, cardiomegaly as a result of ischaemic injury) (Bhatt 2017). The benefit of beta-blockade is currently undisputed for patients with left ventricular systolic dysfunction (LVSD), however the evidence is slightly less compelling for those with preserved left ventricular function (Bangalore et al. 2014; Puymirat et al. 2016).

Atrial fibrillation

Atrial fibrillation (AF) is one of the most common arrhythmias seen in clinical practice. Sympathetic activity can provoke tachyarryhtmias such as AF, where multiple microreentry circuits in the atria produce a rapid but irregular ventricular rate (Waller and Sampson 2017). Beta blockers comprise group II of the Vaughn

Williams classification of antiarrythmic drugs, and reduce the rate of spontaneous depolarisation of nodal tissue in both the sinoatrial and AV nodes, slowing down AV conduction (via adrenoreceptor-sensitive f-channels) and reducing ventricular rate, both at rest and during exercise (DiFrancesco 2010).

In AF, rate control has been shown to be as effective as rhythm control with respect to mortality, and is associated with a lower risk of adverse drug effects, greater cost-effectiveness and a decreased incidence of hospitalisations (Van Gelder et al. 2002; Hagens et al. 2004). Beta blockers were found to achieve rate control in 70% patients when used alone or with digoxin in the AFFIRM trial, which was greater than the success associated with calcium channel blockers (Olshansky et al. 2004). In the RATAF study, however, calcium channel blockers were shown to be more effective than beta blockers for rate control (Ulimoen et al. 2013). Current guidance therefore stipulates that either class of drug can be used first-line for AF depending on patient-specific factors (such as comorbidities and contraindications) (Kirchhof et al. 2016).

Heart failure

The mechanism of action of beta blockers in heart failure is poorly understood, but in addition to their ability to reduce the workload of ischaemic myocardium and inhibit arrhythmia (see above), it has been shown that they can reduce the cardiac remodelling process responsible for disease progression in heart failure (Bhatt 2017). Carvediolol, for example, may reverse the remodelling process by reducing left ventricular volumes and improving systolic function (Khattar 2003). It also has antiproliferative, antioxidant properties and blocks the expression of several genes involved in myocardial damage (Yue et al. 1995).

Historically, beta blockers were considered to be contraindicated in heart failure due to their negative ionotropic properties causing a reduction in cardiac output. There is now clear evidence for their use in all stages of heart failure to confer substantial mortality benefits as well as symptomatic relief in patients with heart

failure. As such, beta blockers are recommended in all patients with heart failure (or LVSD) without contraindications (Packer et al. 1996; The CIBIS-II Investigators 1999; The MERIT-HF Investigators 1999; Packer et al. 2001; Ponikowski et al. 2016).

Although negative ionotropic effects can still be problematic, they may be limited by using small starting doses, uptitrating slowly (e.g. over a number of weeks), and monitoring heart rate, blood pressure and clinical status after each dose increase. Initiation should also follow stabilisation with ACE inhibitor and diuretic therapy in order to limit adverse negative ionotropic effects (NICE 2017).

Hypertension

The reduction in force of myocardial contraction and heart rate results in a decreased cardiac output and therefore a reduction in arterial blood pressure. Beta blockers alter baroreceptor reflex sensitivity, and reduce β_1 mediated renin release from the kidneys (Mann 2017). Reduced renin leads to a reduction in angiotension II and aldosterone, which in turn enhances renal sodium and water loss and lowers blood pressure.

The initial treatment for hypertension no longer includes beta blockers due to their inferior effects on reducing cardiovascular mortality, stroke and myocardial infarction compared to other antihypertensive drugs (Wiysonge et al. 2017). They may, however, still form an important part of antihypertensive treatment in patients who are unable to take first line agents, or who are already established on combination therapy. A summary of recommendations for the use of beta blockers in cardiovascular disease is shown in Table 2.

Precautions for use

Adverse effects

The use of beta blockers is somewhat constrained by their adverse effects, which include sinus bradycardia, worsening of AV node conduction block, intermittent claudication, impotence, depression and nightmares.

Although some beta blockers are cardioselective, they are not entirely specific to β_1 receptors, and may act on β_2 receptors in the bronchial smooth muscle, causing bronchoconstriction. As such, they are contraindicated in patients with asthma. In practice, the benefits of beta blockade may outweigh the risks in those with well-controlled asthma and some clinicians may continue to prescribe them with caution (e.g. at low doses with close symptom monitoring). In patients with irreversible airways disease such as COPD, beta blocker use has not been shown to be detrimental, and as such, should not be withheld where indicated (Salpeter et al. 2005).

Beta blockers binding to adrenoreceptors on vascular smooth muscle can cause vasoconstriction, which may exacerbate symptoms in peripheral vascular disease. The production of insulin is also under adrenergic control, so prescribing beta blockers to people with diabetes may worsen their glucose control and mask symptoms of hypoglycaemia. The abrupt withdrawal of beta blockers should also be avoided due to potential rebound worsening of myocardial ischaemia, infarction or arrhythmias.

Interactions

Although generally beta blockers are a safe group of drug with a large therapeutic index (Brodde and Kroemer 2011), those that are metabolised in the liver (e.g. lipophilic drugs such as metoprolol) may theoretically be subject to more

pharmacokinetic interactions via the CYP450 enzyme group (Flockhart and Tanus-Santos 2002).

All beta blockers may be subject to pharmacodynamic interactions, for example additive effects on lowering blood pressure when used concomitantly with other antihypertensive drugs (e.g. ACE inhibitors), or hypoglycaemia with antidiabetic drugs. Other common drug interactions with beta blockers are included in Table 3.

Conclusion

Beta blockers are an important class of medication that are widely used for a number of cardiovascular indications. Their benefits range from the effective control of heart rate in AF to the significant reduction in mortality in patients with heart failure. Adverse effects of beta blockers should be considered when prescribing them to patients with concomitant conditions (e.g. asthma, diabetes) but should not necessarily exclude their use when their benefit may outweigh the risks. Practitioners have an important role in educating patients with respect to the role of beta blockers in order to optimise their use in the therapy of cardiovascular disease.

Key points

- Adrenaline and noradrenaline are catacholamines that act in the sympathetic nervous system by binding alfa and beta adrenoreceptors.
- Beta blockers act on β_1 receptors in the heart to a decrease in contractility, conduction velocity, heart rate and relaxation rate.
- Beta blockers confer mortality benefits when used post-myocardial infarction and in heart failure. Symptomatic benefits are seen with beta blocker use in angina and heart failure.
- When prescribing and administering beta blockers, potential interactions with other medication should be considered, alongside common adverse effects.

CPD Reflection Questions

- What are the main indications for beta blockers?
- What benefits do beta blockers offer for these indications?
- What are the main side-effects associated with beta blockers and how should they be managed?

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