Beta-blockers are possibly one of the most widely prescribed medications today. They have been used for nearly half a century and may be safely prescribed in all adult age groups (Mulrow et al, 2006). Beta-blockers are used in a number of cardiac and metabolic illnesses as well as being part of psychiatric treatments. There is now an extensive number of beta-blockers available on prescription and these differ in the receptors that they target and in their duration of action.

Cardiac nurses administer beta-blockers daily. It is therefore important that they have a thorough understanding of the basic mechanisms by which these drugs work and be aware of the differences between types. This article aims to provide a basic understanding of the pharmacodynamics and pharmacokinetics of commonly used beta-blockers. The differences between types will be examined using an evidence-based biological paradigm to help the practitioner understand the more subtle and evolving differences which are occurring with the development of new-generation beta-blockers. Practitioners will also be made aware of how important this knowledge is in the safe and effective treatment of cardiac disease and patient care.

Beta-receptors

Beta and alpha-receptors are the main receptors for the sympathetic nervous system. Beta-blockers work by binding to and blocking the beta-receptors which are often referred to as adreno-receptors because they mainly bind adrenaline (epinephrine) and noradrenaline (norepinephrine).

The sympathetic nervous system is part of the autonomic nervous system and regulates bodily function and homeostasis by influencing a large number of organs including the heart, lungs, liver and gut (Figure 1). Sympathetic nerve activity is enhanced in times of stress and results in the so-called ‘fight or flight’ response. The aim of this response is to increase mental awareness and physical activity. These responses increase the energy demand of the body. Activation of the sympathetic nervous system leads to three main changes in the body:

- An increase in heart rate and ventricular contractility. This increases blood flow through the body and therefore improves nutrient delivery
- An increase in respiration rate and dilation of bronchi which enhances oxygen absorption in the blood
- An increase in the breakdown of glucose (glycolysis) and an increase in the breakdown of glycogen into glucose (glycogenolysis), thus increasing the availability of glucose in the blood stream.

The net result of this is that there is a more efficient delivery of glucose and oxygen to various parts of the body, especially the brain and muscles. Once the glucose and oxygen arrive in these areas they are converted by glycolysis to adenosine tri-phosphate (ATP). ATP is the energy molecule of the body and is required in most bodily functions, including muscle contraction and nerve firing.

Receptor subtypes

Alpha and beta-receptors have a number of subtypes which mediate these responses. However, for clinical use, a general understanding of the basic alpha and beta sub-divisions is sufficient.

Although this article is about beta-blockers, to fully understand their function, a succinct review of alpha-receptor function is also necessary. Both the alpha and beta-receptors bind the same substances (adrenaline and noradrenaline) and their binding sites are similar, but not exactly the same, in structure. Therefore when a beta-blocker is given to a patient, although it primarily binds to the beta-receptor, it may also have an effect on the other receptor subtypes.

This effect is much stronger within the group (within the beta-receptor subgroups) than across groups (with alpha-receptor subgroups). Beta-blockers have differing degrees of effect on the alpha-receptor as well as on the beta-receptor subtypes. These differing characteristics

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**Abstract**

After approximately 50 years of development and refinement, there are a significant number of beta blockers available to the clinician today. These medications differ in clinical effect and clearance from the body. This review presents the nurse with the main features of the different types of beta blocker and explains the factors that guide the choice of drug in particular pathologies. This information will give the practitioner an evidence-based understanding of the potential uses and adverse effects which are associated with this class of drugs.

**Key words**

- Beta blocker
- Adrenoceptor antagonist
- Cardiovascular pharmacology
- Ischaemic heart disease
- Heart failure

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determine the therapeutic profile of each specific beta-blocker and influence the choice of one beta-blocker over another in different pathologies.

**Alpha-receptors**

There are two main alpha-receptor subtypes (α₁ and α₂) and the precise allocation of function to each receptor is presently not well described and probably incomplete (Calzada and Artiñano, 2001). However it is generally recognized that α₁ receptors are responsible for vasoconstriction and α₂ receptors are responsible for the regulation of neurotransmitter secretion (noradrenaline) from the presynaptic nerve via a negative feedback mechanism.

**Beta-receptor subtypes**

In comparison, beta-receptors are generally recognized as having three main subtypes. When these bind with adrenaline or noradrenaline, these receptors have different functions at different locations, depending on the subtype of receptor and the organ it is located on.

**β₁ receptors**

β₁ receptors are the predominant type of adrenergic receptor (a receptor that binds adrenaline) in the heart (Bristow, 2000). The receptors:

- Increase sinoatrial nodal firing rate
- Increase atrioventricular node conduction velocity
- Increase myocardial contractility.

**β₂ receptors**

β₂ receptors largely mediate the relaxation of smooth muscle. This includes smooth muscle found in the bronchi, blood vessels and the urinary bladder (Rang et al, 2003).

**β₃ receptors**

β₃ receptors have two main actions: Fat metabolism (Strosberg, 1997) and relaxing the muscle of the urinary bladder. However, there is no firm agreement that these receptors are present in the bladder, most research suggests that it is (Hampel et al, 2004.

**Inhibiting adrenergic effects**

It is now recognized that beta-blockers inhibit the adrenergic effect of beta-receptors by two distinct mechanisms. These mechanisms are antagonism and inverse agonism.

**Antagonism**

Antagonism is an effect associated with a loss of activation of the receptor when the drug binds to either the receptor binding site or to a separate location on the receptor. For instance, beta-blockers bind to the adrenaline binding site. When adrenaline arrives at the receptor it is blocked by the beta-blocker. This prevents the adrenaline from binding to its binding site, resulting in a loss of adrenaline effect. This form of antagonism is known as competitive antagonism (Figure 2). During this process the beta-blocker and the adrenaline are competing for a position on the receptor.

When the drug binds to a site other than the adrenaline binding site, this changes the structure of the receptor. When the structure is altered, the receptor is rendered incapable of activating a response. This form of antagonism is known as non-competitive antagonism (Figure 2).

**Inverse agonism**

Inverse agonism is a relatively new concept in beta-receptor pharmacology. It has been discovered that some beta-receptors, like many other receptors, may be locked in the active state in absence of adrenaline or noradrenaline (Leurs et al, 1998). This subgroup of receptors are therefore constitutively active (Figure 3). An inverse agonist binds to these constitutively active receptors and changes the receptor's structure, thus switching off the activated state and stopping the receptor mediated effect.

Although the clinical relevance of these abnormal receptors is not clearly understood, some studies suggest that the presence of these abnormal receptors may cause a number of pathologies, including hypertension (Bond and Ijzerman, 2006). As such, modulation of these receptors by inverse agonists may be of some clinical benefit in these diseases.
As previously discussed, a single beta-blocker may have a number of affects on a number of beta-receptor and even alpha-receptor subtypes. This includes a possible enhancing or agonistic effect of some receptor subtypes. The ability of a beta-blocker to have an agonistic effect on beta and alpha-receptor subtypes is known as its intrinsic sympathomimetic effect. These features will be discussed in reference to commonly used beta adrenergic blocking medications.

**Beta-blocker generations**

Beta-blockers are commonly sub-divided into three generations of development. These are:

**First generation**

First-generation beta-blockers like propranolol are largely mixed \( \beta_1 \)-\( \beta_2 \) inhibitors. Although sometimes used, these have limited clinical use owing largely to their antagonistic effect on \( \beta_2 \) receptors.

**Second generation**

In contrast, second-generation beta-blockers bind preferentially to the \( \beta_1 \) receptor and are therefore described as beta selective. Of the commonly used beta-blockers, those which select the \( \beta_1 \) receptor include bisoprolol, atenolol, metoprolol and acebutolol. Bisoprolol displays a 14-fold greater affinity for the \( \beta_1 \) receptor than for the \( \beta_2 \) receptor (Baker, 2005). Second generation beta-blockers therefore have limited effect on \( \beta_2 \) receptors and this enables them to be used more safely in patients with asthma.

Although individual patients have varied and unpredictable responses to these drugs, there is now increasing clinical evidence that, at least in cases of short-term use, \( \beta_1 \) selective beta-blockers like bisoprolol and atenolol may be used in mild to moderate reversible airway disease or chronic obstructive pulmonary disease (COPD) (Salpeter et al, 2002; Barnett et al, 2005). However, Salpeter et al (2002) advise that the safe use of such selective preparations in the presence of an acute exacerbation of illness or for long-term administration remains to be established.

Following a meta-analysis of 20 randomized controlled, blinded clinical trials, Salpeter et al (2005) concluded that cardioselective beta-blockers such as atenolol, metoprolol, bisoprolol, practolol, celiprolol and acebutolol did not demonstrate any adverse effect on lung function or respiratory symptoms compared with the placebo. This finding was consistent even when the patient had severe chronic airways obstruction or a reversible obstructive condition. They concluded that a cardioselective beta-blocker should not be withheld from patients with COPD.

Following the clinical implementations of these findings there will conceivably be an increase in the prescription of cardioselective beta-blockers for patients with COPD. However, it must be remembered that these findings are, at present, only relevant to COPD patients. With difficulties in providing a differential diagnosis between severe asthma and COPD, it is important that nursing staff are
vigilant in observing for the possible adverse effects when these drugs are given to patients who have a significant element of broncho-constriction in their disease.

Third generation
Third-generation beta-blockers possess a vasodilatory effect in addition to their beta blockade effect. Beta selectivity of this generation varies.

Carvedilol is a relatively selective (seven-fold greater) beta_1 antagonist, especially at low doses. It also has some effect on the beta_2 receptors as well as a number of alpha_1 receptor blockade properties through which it mediates its vasodilatory effect. For carvedilol this effect is derived from the fact that the clinically available drug is actually a mixture (racemate) of two mirror-image molecules of carvedilol (R-carvedilol and S-carvedilol). Both molecules have equal affinity for the alpha_1 receptor but S-carvedilol has a significantly greater affinity for the beta-receptor (Bartsch et al, 1990).

Bucindolol is a non-selective beta-receptor antagonist with alpha_1 mediated vasodilatory effects. Nebivolol is a novel third-generation beta-receptor antagonist that is highly beta_1 selective (significantly more than bisoprolol) (Bristow, 2005). Nebivolol also has a vasodilatory effect. However, unlike the other drugs mentioned in this group, its vasodilatory effect is mediated by a nitric oxide/L-arginine dependent pathway (Weber, 2005) in a manner similar to nitrates.

Owing to their vasodilatory effect, third generation beta-blockers have been examined in some depth in association with heart failure. The carvedilol or metoprolol European trial (COMET, 2003) concluded that carvedilol was superior to short-acting metoprolol tartrate in reducing all-cause mortality and cardiovascular death. Similarly, the SENIORS trial (Flather et al, 2005) found nebivolol to be effective in significantly reducing cardiovascular death or hospitalization in patients aged over 70 years. The effect of this drug was similar regardless of ejection fraction (EF), age, or gender.

The intrinsic sympathomimetic effect
Beta-blockers that possess an intrinsic sympathomimetic effect such as acebutolol and pindolol (Weber, 2005) have a dual effect by both enhancing the function of the beta-receptors and inhibiting adrenergic stimulation. Consequently, these medications do not diminish the beta adrenergic response to the same magnitude as other beta-blockers which do not possess an intrinsic sympathomimetic effect. Thus, the beta-blocker mediated reduction in

### Table 1. Half-lives of a selection of beta blockers

<table>
<thead>
<tr>
<th>Beta blocker</th>
<th>Half-life (t½)</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol</td>
<td>9–12 hours</td>
<td>Ellison and Gandhi, 2006</td>
</tr>
<tr>
<td>Propranolol</td>
<td>4 hours</td>
<td>Rang et al, 2003</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>3 hours</td>
<td>Rang et al, 2003</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>10 hours</td>
<td>Rang et al, 200</td>
</tr>
<tr>
<td>Esmolol</td>
<td>9 minutes</td>
<td>Wiest, 1995</td>
</tr>
</tbody>
</table>

### Table 2. Recent studies on beta blockade in heart failure

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>Population</th>
<th>New York Heart Association Classification of heart failure/ejection fraction (EF)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>MERIT-HF 1999 failure</td>
<td>Metoprolol Succinate vs Placebo</td>
<td>3991</td>
<td>II–IV</td>
<td>49% relative reduction in death owing to heart</td>
</tr>
<tr>
<td>CIBI –II 1999</td>
<td>Bisoprolol vs Placebo</td>
<td>2647</td>
<td>III–IV</td>
<td>34% reduction in mortality</td>
</tr>
<tr>
<td>COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) (Packer et al, 2001)</td>
<td>Carvedilol vs Placebo</td>
<td>2289</td>
<td>LV ejection fraction (EF) &lt;25%</td>
<td>35% reduction in mortality</td>
</tr>
<tr>
<td>COMET 2003</td>
<td>Carvedilol vs metoprolol</td>
<td>3029</td>
<td>II–IV</td>
<td>34% mortality in carvedilol</td>
</tr>
<tr>
<td>Christmas Study (Bellenger et al, 2004)</td>
<td>Carvedilol vs placebo</td>
<td>34</td>
<td>MRI remodelling study EF +3% carvedilol EF –2% Placebo</td>
<td>40% mortality in metoprolol</td>
</tr>
</tbody>
</table>
heart rate and cardiac output is reduced with beta-blockers that possess an intrinsic sympathomimetic effect.

In addition, the frequently observed beta-blocker mediated increase in vascular resistance is also diminished with beta-blockers which have an intrinsic sympathomimetic effect (Pritchard, 1987; Taylor, 1987). Although these drugs may have an application in hypertension, they are presently contraindicated in treatment regimens after myocardial infarction (MI) as the presence of an intrinsic sympathomimetic effect predicated a considerable reduction in benefits in a meta-analysis of data from a large group of clinical trials (Freeman et al, 1999). In addition, these beta blockers have been shown to precipitate heart failure in high risk patients (Pritchard, 1987).

As in cases of asthma, the use of beta-blockers in patients with diabetes mellitus has been controversial. Glucose metabolism is affected by a number of adrenergic receptors including the beta_2, beta_3, alpha_1 and alpha_2 receptors. Evidence suggests a moderate association between the presence of a specific genetic mutation (polymorphism) of the beta_2 and the beta_3 receptor with insulin resistance in Asian, obese and diabetic populations (Masuo et al, 2005; Park et al, 2005; Zhan and Ho, 2005). Therefore beta blockade, especially non-selective, could influence glucose metabolism. However, few clinical trials have examined this aspect of the beta-blocker side effect profile.

The Gemini trial (Bakris et al, 2004) compared the metabolic effects of carvedilol and metoprolol in patients with type 2 diabetes mellitus and hypertension on glycaemic control and insulin response in 1235 patients. It was found that both beta-blockers were tolerated well and that metoprolol was associated with a small but statistically significant increase in HbA_1c over the 35-week study period. Furthermore, carvedilol displayed a small but significant improvement in insulin resistance compared to metoprolol (Bakris et al, 2004). This study indicates the safety of using beta-blockers in patients with type 2 diabetes mellitus, although further examination of the long-term effects of these medications on glycaemic control are required.

The central nervous system

Beta-blockers have a number of effects on the central nervous system. The prototype beta-blocker propranolol is highly fat soluble. As a rule, fat soluble drugs diffuse through barrier membranes including the gut and blood-brain barriers with ease (Khan, 2002). Owing to its ability to permeate the blood-brain barrier, propranolol has a significant effect on adrenergic nerves in the brain. These nerves’ major function is to moderate mental awareness and alertness. Therefore the administration of propranolol reduces mental alertness and may cause drowsiness. Newer classes of beta-blocker, such as atenolol, tend to be more water soluble and therefore do not permeate the blood-brain barrier with such ease. Thus these drugs are associated with fewer effects on the central nervous system such as drowsiness, nightmares and sleep disturbances (Joint Formulary Committee, 2005).

Pharmacokinetics

The main pharmacological parameters that may determine choice of beta-blocker have been explored. The other main consideration to examine is the pharmacokinetic profile of the beta-blocker. This profile is determined by its physico-chemical characteristics which determine how the drug is absorbed, distributed, metabolized and excreted from the body. These pharmacokinetic processes determine the duration of action of these drugs. The duration of effect of a drug is measured pharmacokinetically as its half-life. A half-life is the time it takes the body to reduce the plasma concentration of a bolus of medication by half (Table 1).

It is apparent that beta-blockers such as carvedilol require less frequent dosing than metoprolol. Esmolol has an extremely short half-life (average 9 minutes) and this makes it particularly suitable for intra-operative use.

Interactions

Drug interactions occur when drugs compete or overload pharmacokinetic processes. Of these processes, renal clearance as well as enzymatic liver metabolism are of significant importance. In cases of hepatic and renal function impairment, practitioners are often required to re-adjust dosing regimens owing to a change in drug metabolism or clearance. Kyoko et al (2006) have recently demonstrated a drug interaction between carvedilol and amiodarone that raised the beta blocking (S-carvedilol) component of the carvedilol mixture. This interaction resulted from a competition between both drugs for the same metabolic enzyme cytochrome 2C9 in the liver. In addition, by blocking the S-carvedilol component the beta-blockade effect of this drug could be increased, possibly resulting in the development of adverse effects such as bradycardia and hypotension. It is apparent therefore that nurses need to monitor drug effects closely in patients for whom renal or hepatic impairment may develop.

Heart failure

Use of beta-blockers in heart failure is of considerable clinical benefit. However it remains problematic, in spite of the recommendations by the National Institute for Health and Clinical Excellence (NICE) (2001) and the American Heart Association (Ellison and Gandhi, 2006). The NICE recommendations include the commencement of beta-blocker therapy while a patient is still in hospital and these regimes should be considered for the long-term if there is no clear reason to stop treatment (NICE, 2001). There have been a number of studies which show the benefits of beta blockade in heart failure (Table 2).

These studies showed that beta-blockers provide a significant improvement in survival rates compared to the placebo. The purported negative inotropic effect of a beta-blocker theoretically should reduce the ejection fraction of a patient with heart failure. This theory appears to present a significant hindrance to prescribing beta-blockers in heart failure. There are also considerable levels of caution in prescribing these drugs in areas such as pri-
Cardiac side effects
Cardiac side effects which may be expected include brady-cardia, and atrioventricular conduction blocks. If the patient is older, fibrosis may influence proper conduction in the heart and this may further increase these risks. In such cases beta-blockers may also lead to abnormalities in the function of the sino-atrial node, leading to the so-called sick sinus syndrome (Marriot and Conovor, 1998).

Erectile dysfunction
Although the association of beta blockade with erectile dysfunction has been much discussed, the BHAT study (1982) found little difference in erectile function between the study group (propranolol) and control. The appearance of this side effect is relatively rare in randomized control studies (Ellison and Gandhi, 2005). The use of nebivolol has been suggested to be beneficial in the presence of this side effect, potentially owing to its nitric oxide related vasodilatory effects (Doumas et al, 2006). However, until now, there has been a limited evidence-base for its use.

Co-administration
Co-administration of other medications that may effect cardiac function like antihypertensives or antiarrhythmics may have an additive effect with beta-blockers. For example, anti-arrhythmics tend to increase the effect of beta-blockers (Khan, 2005). This effect may be stronger with certain antiarrhythmics such as sotalol which is a beta-blocker in its own right, and the drug interaction between amiodarone and carvedilol, as identified above. Drugs like verapamil have a significant negative dromotropic effect (reduced conduction velocity) particularly on the atrioventricular node. Thus, a combination of verapamil and a beta-blocker is, in many cases, contraindicated. Similar caution should be exercised with a combination of diltiazem and beta-blockers because diltiazem also has a significant negative dromotropic effect on cardiac conduction.

Role of the nurse
It is apparent that the nurse has a pivotal role in the successful commencement and maintenance of a beta-blocker regimen. Although advanced knowledge of these medications is of great benefit for more autonomous nurse practitioners, all nursing staff, including students, need to be aware of the potential use and adverse effects of these medications. Because beta blockers are rarely used in isolation the nurse should monitor for the adverse effects described above. The majority of the effects of beta-blockers which are administered on their own or in combination with other drugs will result in a continuous or intermittent drop in blood pressure. This will clinically manifest as dizziness and syncope or postural hypotension. The nurse needs to remain extra diligent when administering prescribed beta-blockers to patients who have underlying respiratory disease, at least until the differences in response for each class of beta-blocker have been clinically established.

In addition, the nurse should regularly monitor the blood glucose levels of patients who are at risk of blood

Implications
The use of beta-blockers in cardiac illness has been long recognized by a number of national and international regulating and governing bodies, including the European Cardiac Society, the British Cardiac Society, the British Hypertension Society and the American College of Cardiologists. The National Institute for Health and Clinical Excellence (NICE) has published a number of guidelines that suggest the early introduction of beta-blocker therapy in heart failure and after myocardial infarctions (NICE, 2001).

Side effects
The use of beta-blockers has become more widespread and there is an increasing body of evidence that suggests their safety, even in conditions such as obstructive airway disease where their use was previously contraindicated.

The nurse will be the professional who will most often administer or witness the administration of these medications and therefore it is his/her responsibility to monitor the therapeutic effect of a medication as well as the side effects.

Underlying pathlogy
The adverse effects of beta-blockers in respiratory disease and diabetes have been addressed. Side effects often depend on the type of drug being administered and the patient's underlying pathology. For example, when considering the use of beta-blockers in the cases of ischemia, the aim is to reduce the cardiac workload by reducing adrenergic stimulation. As the beta-blocker has an effect on the sino-atrial node, on cardiac conduction and on ventricular contractility, the possible side effects of this medication may be multiple. The nurse needs to monitor these effects in patients, especially when the drug is commenced or when the patient becomes pharmacokinetically unstable in cases such as patients with renal or liver impairment.

mary care where the patient's response to the drug cannot be monitored closely and acute changes in his/her physical state may affect the manner in which the drugs are metabolized or cleared from the body.

However, the studies above clearly indicate the benefit of using these drugs in cases of heart failure. Furthermore, the use of beta-blockers should improve as this information spreads among clinicians. Importantly Ansari et al (2003) have shown that the use of a nurse facilitator in improving the use of beta-blockers in patients with heart failure was a successful strategy when compared to clinical reminders and different forms of patient education, which were of limited value. This study cited a number of barriers which hindered the initial prescription and future titration of beta-blockers in patients with heart failure. Such barriers included a lack of awareness, inertia of previous practice, lack of agreement about drug choice and dose and lack of set times for doses. Ansari et al (2003) suggested that the primary care practitioners involved were more successful in improving beta-blocker therapy because they were more able to overcome these obstacles than their clinical counterparts.
Increasing clinical evidence suggests the possibility of using beta-blockers in, until recently, contraindicated circumstances such as asthma and heart failure.

Key Points

- Beta blockers are one of the most commonly used medications in the care of cardiac patients.
- Beta blockers may be cardiac specific or have a mixed effect on the body.
- Increasing clinical evidence suggests the possibility of using beta-blockers in, until recently, contraindicated circumstances such as asthma and heart failure.
- In the interests of patient safety it is the nurse’s responsibility to be aware of potential side effects of beta-blockers on the patient.

Conclusions

Beta-blockers are a significant pharmacological entity in the care of cardiology patients. The choice of beta-blocker is determined by a particular beta-blocker's pharmacodynamic as well as its pharmacokinetic profile. There is an increasing body of evidence which suggests that the development of more specific beta-blockers has widened their sphere of clinical use. They can now be used in areas where they were previously contraindicated. Nurses have an important role to play in optimizing the safe use of beta-blockers in the clinical environment.


