Pharmacology

Drugs affecting the autonomic nervous system

Raghavendran Krishnaiyan
Jonathan P Thompson

Abstract
The autonomic nervous system (ANS) is a complex system of the nervous and humoral mechanisms that modulates the function of the autonomous or visceral organs. Autonomic control of several organs aims to maintain homeostasis in health. Many drugs used in clinical practice may have either primary or secondary effects on the function of the ANS.

Keywords Automation nervous system; catecholamines; parasympathetic; sympathetic

Royal College of Anaesthetists CPD Matrix: 1A02

The autonomic nervous system (ANS) is divided on anatomical, physiological and pharmacological grounds into sympathetic (SNS) and parasympathetic (PNS) divisions (Tables 1 and 2). Transmission at SNS and PNS preganglionic neurons is mediated by acetylcholine (ACh) acting at nicotinic receptors. However, neuronal activity at preganglionic neurons is modulated by other neuropeptides including enkephalin, substance P, serotonin and catecholamines. Postganglionic transmission in SNS neurons at effector organs is mediated by noradrenaline, acting via specific adrenergic receptors, except for sweat glands, pilo-erector muscles and some blood vessels which are cholinergic. SNS neurons also respond to circulating catecholamines. Adrenergic receptors are classified into three major types (α1, α2, and β) with at least three further subtypes in each class. Two subtypes of β-receptor (β1 and β2) are well defined on functional, anatomical and pharmacological grounds and a third β-receptor subtype, β3, is found in adipocytes, skeletal and ventricular muscle, and the vasculature. Dopaminergic (D) receptors are now classified separately from adrenoceptors but are included here as there is overlap in their actions and response to exogenous and endogenous catecholamines. There are five subtypes of D receptors (D1–D5) belonging to two subfamilies: D1-like and D2-like. Postsynaptic D1-like receptors mediate vasodilatation in vascular smooth muscle of the renal, splanchic, coronary and cerebral circulations; D2-like receptors are widespread in the CNS. ACh is the primary neurotransmitter at postganglionic PNS neurons, though γ-aminobutyric acid (GABA) and serotonin can also affect transmission here. The postganglionic PNS effects of ACh are mediated by five subtypes of muscarinic receptors (M1–5). Postganglionic muscarinic and adrenergic receptors are coupled to membrane-bound G-proteins and elicit a response through second and third messenger systems that vary with receptor subtype (Table 1).

DRUGS ACTING ON THE SYMPATHETIC NERVOUS SYSTEM

Drugs with effects that mimic stimulation of SNS or adrenal medullary discharge are termed sympathomimetics; drugs that antagonize the sympathetic nervous system effects are called sympatholytics. Other more recent methods of modulating the ANS (e.g. implantable carotid sinus stimulators or renal sympathetic-nerve ablation procedures) have been introduced for the treatment of drug-resistant hypertension; these are outside the scope of this article.

Sympathomimetics
Sympathomimetics can mimic SNS stimulation either by acting directly on adrenoceptors (e.g. catecholamines, phenylephrine, and methoxamine) or indirectly by stimulating release of noradrenaline from nerve endings (e.g. amphetamine) and also by both mechanisms (e.g. dopamine, ephedrine and metaraminol). Sympathomimetics can be classified pharmacologically according to their structure (catecholamine/non-catecholamine), origin (endogenous/synthetic) and site of action (adrenoceptor/non-adrenoceptor).

Catecholamines
Catecholamine drugs can be endogenous or synthetic; all have very short half-lives in vivo. They are immediately inactivated in the gut by monoamine oxidase (MAO) enzymes and the usual route of administration is parenteral, either by intravenous bolus or infusion; dose is titrated to clinical effect. Choice of catecholine depends on the clinical indication, desired therapeutic response and duration of action.

Endogenous catecholamines: the endogenous catecholamines (dopamine, noradrenaline and adrenaline) are synthesized from the essential amino acid phenylalanine (Figure 1).

Adrenaline (epinephrine) — adrenaline is the principal catecholine (80–90%) synthesized by the adrenal medulla and is a potent, non-selective sympathomimetic with agonist activity at both α and β receptors. It can be given intravenously (IV), intramuscularly (IM) or via nebulizer or tracheal tube. In non-emergency situations, adrenaline should be administered IM to

Learning objectives
After reading this article you should be able to:
• identify five sympathomimetic drugs, their indications and doses
• identify five sympatholytic drugs, their indications and doses
• explain the biosynthesis of endogenous catecholamines

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reduce the risk of cardiac arrhythmias and intense vasoconstriction. In emergency situations (e.g. cardiac arrest, peri-arrest situations, anaphylaxis) the IV route is indicated.

The effects of adrenaline are dose-dependent. Algorithms for cardiac arrest and anaphylaxis are available from http://www.resus.org.uk.¹ The usual IM dose is 0.5–1.0 mg (0.5–1.0 ml of 1:1000 [1 mg/ml] solution) and IV dose is 100 μg increments (1 ml of 1:10000 [0.1 mg/ml]).

In very low doses, the β₂ effects predominate and bronchodilation, vasodilation in skeletal muscle and splanchnic arterioles is evident as a decrease in arterial pressure with a widened pulse pressure. At higher infusion rates or bolus doses, α effects are more evident: renal and skin vasoconstriction occurs though increased systemic vascular resistance leads to increases in coronary and cerebral blood flow.

Adrenaline is incorporated into local anaesthetic solutions to enhance their actions by decreasing systemic absorption and prolong the duration of action. Adrenaline is also used as a topical vasoconstrictor to achieve local haemostasis and in the treatment of wide-angle glaucoma.

Noradrenaline (norepinephrine) — noradrenaline is synthesized mainly in the postganglionic sympathetic nerve endings and also from adrenal medulla. Noradrenaline acts primarily on α receptors to cause intense arteriolar and venous vasoconstriction, usually accompanied by a reflex bradycardia, but noradrenaline is also an agonist at β and D receptors. The main indication for noradrenaline is in sepsis with hypotension refractory to fluid therapy, when systemic vascular resistance is low. Noradrenaline increases systolic and diastolic pressures with associated rise in pulmonary artery and central venous pressures. Cardiac output may be unchanged but myocardial oxygenation is increased. Noradrenaline is administered IV as an infusion through a central vein. The usual concentration is a solution of 100 μg/ml administered at a dose of 0.05–1.5 μg/kg/minute.

Dopamine — dopamine is the natural precursor of adrenaline and noradrenaline (Figure 1). It stimulates α, β and dopamine (D₁ and D₂) receptors in a dose-dependent manner and also acts by release of noradrenaline from adrenergic nerve endings. Dopamine receptors are present throughout the body but concentrated in the CNS (basal ganglia, chemoreceptor trigger zone and the pituitary) with receptors also in the splanchnic and renal circulations.

At doses below 3 μg/kg/minute, the main effect is renal and mesenteric vasodilatation mediated through activation of D₁ receptors. Renal and splanchnic blood flow increase,² thereby increasing glomerular filtration, urine production and sodium excretion. Between 5 and 10 μg/kg/minute, β₁ effects predominate causing an increase in contractility, heat rate and cardiac output. Systolic pressure is also usually increased. At doses above 15 μg/kg/minute, α-mediated vasoconstriction predominates causing decreases in splanchnic and renal blood flow with increased risk of arrhythmias.

Dopamine has been used for the treatment of cardiogenic shock, refractory congestive cardiac failure and after cardiac arrest. Its effects in these situations are more evident: renal and skin vasoconstriction occurs though increased systemic vascular resistance leads to increases in coronary and cerebral blood flow. At lower doses, Dopamine causes an increase in diastolic pressure with little change in heart rate and cardiac output.

Table 1

<table>
<thead>
<tr>
<th>Adrenoceptors and acetylcholine receptors</th>
<th>Adrenoceptors</th>
<th>Selective antagonist e.g.</th>
<th>Acetylcholine receptors</th>
<th>Selective antagonist e.g.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptor Location</td>
<td>Second messenger</td>
<td></td>
<td>Location</td>
<td>Second messenger</td>
</tr>
<tr>
<td>α₁</td>
<td>Smooth muscle, skeletal muscle, cardiac muscle, liver</td>
<td>IP₃ (G₃)</td>
<td>Prazosin, doxazosin, indoramin</td>
<td>M₁</td>
</tr>
<tr>
<td>α₂</td>
<td>Pre-synaptic sympathetic nerves, CNS, platelets</td>
<td>↓ cAMP (G₃)</td>
<td>Yohimbine, idazoxan</td>
<td>M₂</td>
</tr>
<tr>
<td>β₁</td>
<td>Heart</td>
<td>cAMP (G₃)</td>
<td>Atenolol, metoprolol, bisoprolol, esmolol</td>
<td>M₄</td>
</tr>
<tr>
<td>β₂</td>
<td>Smooth muscle, skeletal muscle, cardiac muscle, liver</td>
<td>cAMP (G₃)</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>β₃</td>
<td>Fat, subcutaneous tissue</td>
<td>cAMP (G₃)</td>
<td>M₅</td>
<td>Mucarinic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N₁ (muscle receptors)</td>
<td>N₂ (neuronal receptors)</td>
</tr>
</tbody>
</table>

Stimulation of β₁-3 receptors, results in the activation of guanosine triphosphate (GTP)-binding proteins, Gₛ which in turn activates adenylate cyclase enzymes and cause the generation of cyclic adenosine monophosphate (cAMP) to mediate the associated altered cell function. On the other hand α₁, M₁ and M₄ receptors interact with Gₛ proteins to inhibit adenylate cyclase and hence cAMP. In contrast, stimulation of α₂, M₂ and M₅ receptors causes interaction with another GTP-binding protein, Gₛ to activate membrane-bound phospholipase C. This leads to production of inositol triphosphate (IP₃) by hydrolysis of phosphatidylinositol biphosphate (PIP₂) and brings about changes in intracellular Ca²⁺ levels. Nicotinic receptors are associated with non-selective ion channels that open up on their activation to effect changes. CNS, central nervous system.

Table 1

<table>
<thead>
<tr>
<th>Receptor Location</th>
<th>Acetylcholine receptors</th>
</tr>
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<tbody>
<tr>
<td>Location</td>
<td>Second messenger</td>
</tr>
<tr>
<td>α₁</td>
<td>Smooth muscle, skeletal muscle, cardiac muscle, liver</td>
</tr>
<tr>
<td>α₂</td>
<td>Pre-synaptic sympathetic nerves, CNS, platelets</td>
</tr>
<tr>
<td>β₁</td>
<td>Heart</td>
</tr>
<tr>
<td>β₂</td>
<td>Smooth muscle, skeletal muscle, cardiac muscle, liver</td>
</tr>
<tr>
<td>β₃</td>
<td>Fat, subcutaneous tissue</td>
</tr>
</tbody>
</table>

¹ Stimulation of β₁-3 receptors, results in the activation of guanosine triphosphate (GTP)-binding proteins, Gₛ which in turn activates adenylate cyclase enzymes and cause the generation of cyclic adenosine monophosphate (cAMP) to mediate the associated altered cell function. On the other hand α₁, M₁ and M₄ receptors interact with Gₛ proteins to inhibit adenylate cyclase and hence cAMP. In contrast, stimulation of α₂, M₂ and M₅ receptors causes interaction with another GTP-binding protein, Gₛ to activate membrane-bound phospholipase C. This leads to production of inositol triphosphate (IP₃) by hydrolysis of phosphatidylinositol biphosphate (PIP₂) and brings about changes in intracellular Ca²⁺ levels. Nicotinic receptors are associated with non-selective ion channels that open up on their activation to effect changes. CNS, central nervous system.

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surgery, and in low doses in an attempt to preserve renal blood flow in the critically ill. Dopamine infusions are associated with decreased prolactin secretion and the use of dopamine has declined (Table 3).

**Synthetic catecholamines**

**Dobutamine** — dobutamine is a synthetic catecholamine similar in structure to dopamine. Dobutamine acts mainly at $\beta_1$ receptors but also has some activity at $\alpha$ receptors. It has no effect on $\alpha_2$ receptors. Dobutamine increases cardiac contractility, sino-atrial node automaticity and increases conduction velocities in atria, ventricles and through the atrioventricular (AV) node.

Its main effect is to increase cardiac output through increases in contractility and heart rate ($\beta_1$). There is also a degree of afterload reduction mediated through $\beta_2$ stimulation which is useful in treating patients with primary cardiac failure but vasodilatation is problematic in sepsis so in this situation dobutamine is often used in conjunction with noradrenaline. Dobutamine is administered as an IV infusion, the usual dose being 0.5–40 $\mu$g/kg/minute.

**Dopexamine** — dopexamine is a synthetic dopamine analogue that stimulates $\beta_2$, $D_1$ and $D_2$ receptors and also inhibits neuronal noradrenaline reuptake. $\beta_2$ effects cause a decrease in systemic vascular resistance producing vasodilatation in skeletal muscle; dopaminergic effects are renal and mesenteric arteriolar dilatation (increasing gut perfusion). Coronary and cerebral blood flow is increased through vasodilatation. Dopexamine is used in the treatment of acute primary cardiac failure and low cardiac output states. The dose of dopexamine is 0.5 $\mu$g/kg/minute up to a maximum of 6 $\mu$g/kg/minute.

**Isoprenaline** — isoprenaline acts solely on $\beta$ receptors. Effects on $\beta_1$ receptors cause an increase in automaticity and heart rate (arrhythmias are common); $\beta_2$ effects produce vasodilatation and a decrease in systemic vascular resistance allowing an increased venous return: this along with increased contractility of the heart increases cardiac output. Systolic pressure increases but diastolic pressure falls, which can lead to hypoperfusion of the coronary circulation and decreased cardiac oxygen delivery. Other $\beta_2$ effects are bronchodilatation and mast cell stabilization but isoprenaline has been superseded in the treatment of asthma by specific $\beta_2$ agonists with fewer adverse cardiac effects. It may be used for the temporary treatment of bradycardias or atrioventricular block associated with low cardiac output because it increases heart rate and conduction by a direct action on the subsidiary pacemaker. The usual infusion rate is 0.5–8.0 $\mu$g/minute.

**Non-catecholamine sympathomimetic drugs**

**Ephedrine** — ephedrine is a naturally occurring sympathomimetic amine which acts both directly (stimulating both $\alpha$ and $\beta$ receptors) and indirectly (by causing release of noradrenaline from sympathetic nerve terminals). Ephedrine increases heart rate, cardiac output, cardiac oxygen demand, cerebral and coronary blood flow. It also induces bronchodilatation and tachypnoea. These effects last longer (onset within 1 minute and lasting up to 1 hour) than endogenous catecholamines as ephedrine is not metabolized by catechol-O-methyltransferase (COMT) and MAO.

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**Table 2**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Receptor</th>
<th>Sympathetic Effect</th>
<th>Parasympathetic Receptor</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>$\beta_1$, $\beta_2$, $\alpha$ and $D_1$</td>
<td>↑ Heart rate, force of contraction, excitability</td>
<td>M_2</td>
<td>↓ Heart rate</td>
</tr>
<tr>
<td>Arteries</td>
<td>$\alpha_1$, $\alpha_2$, $\beta_1$, $\beta$</td>
<td>Vasoconstriction, Coronary vasodilatation, Skeletal muscle vasodilatation</td>
<td>M</td>
<td>Vasodilatation in skeletal muscle, skin, pulmonary and coronary circulations</td>
</tr>
<tr>
<td>Veins</td>
<td>$\alpha_1$, $\alpha_2$, $\beta_2$</td>
<td>Vasoconstriction</td>
<td>M</td>
<td>Glycogen synthesis</td>
</tr>
<tr>
<td>Lungs</td>
<td>$\alpha_1$, $\alpha_2$, $\beta_2$</td>
<td>Bronchoconstriction, Vasodilatation, ↑ secretions</td>
<td>M</td>
<td>Bronchoconstriction</td>
</tr>
<tr>
<td>Kidneys</td>
<td>$\beta$</td>
<td>Renin secretion</td>
<td>M</td>
<td>Glycogen synthesis</td>
</tr>
<tr>
<td>Liver</td>
<td>$\beta_2$ and $\alpha$</td>
<td>Glycogenolysis, Gluconeogenesis</td>
<td>M</td>
<td>Glycogen synthesis</td>
</tr>
<tr>
<td>Bladder</td>
<td>$\beta_2$ and $\alpha$</td>
<td>Detrusor relaxation, Sphincter contraction</td>
<td>M</td>
<td>Detrusor contraction</td>
</tr>
<tr>
<td>Uterus</td>
<td>$\alpha_1$, $\beta_2$</td>
<td>Myometrial contraction, Myometrial relaxation</td>
<td>M</td>
<td>Detrusor relaxation</td>
</tr>
<tr>
<td>Eye</td>
<td>$\alpha_1$</td>
<td>Mydriasis, ciliary muscle relaxation</td>
<td>M</td>
<td>Miosis, ciliary muscle contraction</td>
</tr>
</tbody>
</table>

The five different muscarinic receptor subtypes (M1–5) have been classified by the use of selective radioactively labelled agonist and antagonist substances. Note that in some cases the receptor subtype is not known.
Doses vary from 3 to 30 mg IV but above this tachyphylaxis develops due to depletion of noradrenaline from nerve terminals. Ephedrine easily crosses the blood-brain barrier and is used in the treatment of narcolepsy and nocturnal enuresis. Ephedrine was used widely in obstetric anaesthesia as uterine blood flow is relatively maintained. However, it crosses the placenta to cause increased fetal metabolic rate and metabolic acidosis so has been superseded by phenylephrine in this context.

Phenylephrine is a selective α1 agonist; the main effect of phenylephrine is to cause vasoconstriction. Other effects include mydriasis. Phenylephrine can be administered via several routes including oral, nasal (as a decongestant), topical eye drops and IV. MAO is present in the gastrointestinal tract and the bioavailability of phenylephrine is approximately 38%. Phenylephrine has largely replaced ephedrine as pressor of choice in obstetric anaesthesia. Phenylephrine can be administered as a bolus of 50–100 μg IV or as an infusion 50–100
µg/ml. Effects occur within 1 minute with a duration of up to 45 minutes after a bolus. Phenylephrine has no inotropic or chronotropic effects directly but should be used with caution as marked reflex bradycardia can occur.

Metaraminol—metaraminol is a direct- and indirect-acting α- and β-agonist whose α effects predominate. The main effect of metaraminol is to increase arterial pressure through α stimulation which increases systemic and pulmonary arterial pressures; cerebral and renal blood flow decrease and the drug causes contraction of the pregnant uterus. The dose range is 0.5–5 mg IV titrated slowly as reflex bradycardia leading to cardiac arrest has been reported. Effects are seen within 2 minutes and duration is 20–60 minutes.

Clonidine acts at central and peripheral α₂ receptors as a partial agonist (some α₂ activity α₂:α₁ >200:1) and as a full agonist at central imidazoline receptors. Transient hypertension and bradycardia can occur after IV injection through stimulation of the vascular α₂ receptors followed by centrally mediated hypotension. Clonidine IV 2–3 µg/kg attenuates sympathetic responses during anaesthesia whilst 1–2 µg/kg neuraxially increases the potency and duration of analgesic block. Clonidine is absorbed well orally with peak plasma levels at 60–90 minutes.

Dexmedetomidine is a full agonist at central and peripheral α₂ receptors (α₂: α₁ >1600:1), with a selectivity 8–10-fold greater than clonidine for α₂ receptors. Dexmedetomidine has similar effects to clonidine on sympathetic responses under anaesthesia, has significant opioid-sparing effects and is used in the treatment of intractable neuropathic pain. Dexmedetomidine may also be administered as an infusion (dose range 0.2–0.7 µg/kg/hour) for sedation in the intensive care unit. Its perceived advantages include the production of cooperative sedation with limited respiratory depression though it is not recommended for more than 24 hours of continuous infusion. A biphasic blood pressure response and bradycardia can occur, similar to clonidine.

Fenoldopam is a selective D₁ agonist. Effects include increased renal blood flow, diuresis, natriuresis and peripheral vasodilation. It has been used in the treatment of hypertensive crises (IV infusion 0.03–0.1 µg/kg/min). After stopping the infusion there is no rebound hypertension unlike other vasodilators.

Sympatholytic drugs

Ganglion blockers
These non-selectively block post-synaptic transmission in both the SNS and PNS. Examples include hexamethonium and trimetaphan. Effects include dry mouth, urinary retention, vasodilation and hypotension. Tachyphylaxis is problematic and they have been superseded by newer more selective drugs.

α receptor antagonists

Non-selective α antagonists: phentolamine, phenoxybenzamine and tolazoline produce a postural hypotension with a reflex tachycardia and abdominal side effects such as cramps and diarrhoea. Phentolamine is a competitive antagonist used in the diagnosis and treatment of phaeochromocytoma and the treatment of acute hypertensive crises. Usual dose is 2–5 mg IV to control hypertensive crises.

Phenoxybenzamine is occasionally used in the treatment of hypertensive crises, Raynaud’s disease and the perioperative management of phaeochromocytoma. It binds irreversibly and competitively to α receptors (effects last several days) to produce orthostatic hypotension with a consequent tachycardia. Other effects include sedation, miosis and marked nasal mucosal congestion. The oral dose is 10–60 mg/day and IV as an infusion of 10–40 mg over 1 hour.

Selective α₂ antagonists: tamsulosin stimulates prostatic α₁₃ receptors rather than vascular α₁ receptors. It is used to treat benign prostatic hyperplasia (BPH) as smooth muscle relaxation allows easier urinary flow. Adverse effects include reactions to the sulphur moiety of the drug and a condition known as ‘floppy iris syndrome’.

Indoramin is a selective α₁ adrenoceptor antagonist acting on the heart and therefore does not induce a reflex tachycardia.

Doxazosin is a selective α₁ antagonist used to treat BPH and hypertension. Its duration of action is prolonged compared to earlier drugs such as prazosin and it has a better side effect profile in terms of erectile function when used in BPH.

β adrenoceptor antagonists
β blockers are classified according to their receptor selectivity (β₁ or β₂). All β blockers are all competitive antagonists and bind avidly to their specific receptors. Despite this it is possible receptor stimulation can occur if endogenous catecholamine concentrations are high. β blockers decrease cardiac contractility and automaticity, and increase refractory times at the sinoatrial (SA) and AV nodes. Heart rate, cardiac work, propensity to arrhythmias, risk of myocardial ischaemia and arterial pressure are all reduced. Non-cardiac effects include increased airways and peripheral vascular resistance; these can lead to bronchospasm and worsen symptoms of peripheral vascular disease. Some β blockers act as partial agonists, membrane stabilizers and also stimulate other receptors (e.g. carvedilol).

Non-selective β antagonists
Propranolol binds to both β₁ and β₂ receptors and also exhibits a membrane stabilizing effect through its action on Na⁺ channels. It has no sympathomimetic actions, is highly lipid-soluble and crosses the blood–brain barrier. Propranolol is used in the treatment of hypertension, angina, the sympathetic manifestations of anxiety, thyrotoxicosis, portal hypertension, hypertrophic obstructive cardiomyopathy and migraine. It is administered orally (30–320 mg/day) in two or three divided doses, or IV 1–10 mg titrated to response.

Carvedilol is a β₁, β₂ blocker which is also an antagonist at α₁ receptors. Cardiac work and afterload are reduced and it is used to treat congestive heart failure.

Labetalol is a mixed α and β blocker primarily used in the treatment of hypertensive crises particularly pregnancy-induced hypertension and pre-eclampsia. It is available as an oral formulation (dose up to 2.4 g/day) or IV infusion of 2 mg/minute. Bolus IV doses can be administered (e.g. 20 mg over 2 minutes). The ratio of β to α activity varies with route of administration, oral (3:1) and IV (7:1). Adverse effects include insomnia, drowsiness and rarely respiratory distress.

Selective β₁ blockers
Atenolol is a relatively cardioselective (β₁) β blocker which is administered orally (50–100 mg/day) or IV (2.5–10 mg,
maximum 1 mg/minute). Atenolol is predominantly excreted unchanged in the urine and therefore the dose must be adjusted in patients with renal disease.

Metoprolol is used to treat hypertension and in the treatment/prevention of angina. It is available in either oral (50% bioavailability), or IV preparations. There is no intrinsic sympathomimetic activity. Oral doses vary with indication between 100 and 450 mg/day. Slow-release preparations are available.

Bisoprolol exhibits almost twice the selectivity for β1 receptors compared to atenolol and propanolol. Bisoprolol also inhibits the secretion of renin. The oral dose is 2.5–20 mg/day (oral bioavailability 90%) and metabolism is via hepatic and renal systems to inactive metabolites. The half-life of bisoprolol is approximately 10–12 hours.

Esmolol is a short-acting β1 selective blocker used in the treatment of supraventricular tachyarrhythmias (atrial flutter and fibrillation) and perioperative hypertension. Esmolol is metabolized by red cell esterases to produce methanol and a weaker active metabolite. It is administered IV as a bolus (0.5–2.0 mg/kg) or an infusion (25–500 µg/kg/minute) with clinical effects within 2 minutes and duration of action of approximately 10 minutes.

PARASYMPATHETIC DRUGS

Agonists

Pilocarpine is a muscarinic agonist used topically in the treatment of glaucoma.

Antagonists

Atropine is a competitive muscarinic antagonist with widespread dose-dependent effects which include increased heart rate, decreased bladder tone, decreased salivary secretions, increased intra-ocular pressure and mydriasis. Atropine is administered IV in a dose between 0.6 and 3.0 mg to counter intense vagal stimulation (the dose in children is 20 µg/kg). At very low doses there is a paradoxical bradycardia thought to be mediated by M2 receptor antagonism centrally in the CNS (Bezold–Jarisch effect). The therapeutic dose effects are mediated by M3 receptors, whilst at high doses, excitation/sedation, hallucinations, ventricular arrhythmias or hyperthermia can occur.

Hyoscine is available in two forms: hydrobromide and butylbromide. Hyoscine butylbromide is used as an antispasmodic (genitourinary and gastrointestinal). The hydrobromide form increases heart rate less but is a more effective antispasmodic than atropine and causes problems in the elderly, as it crosses the blood–brain barrier causing confusion, sedation and ataxia (central anticholinergic syndrome). Hyoscine is used as an antiemetic, especially for motion sickness (transdermal patch application).

Glycopyrrolate is a quaternary ammonium compound with similar effects to atropine but is approximately five times more potent as an antispasmodic. Glycopyrrolate does not cross the blood–brain barrier so has no CNS effects. It is used to prevent bradycardia caused by neostigmine as it has a similar onset and duration of action. The dose of glycopyrrolate in adults is 0.2–0.4 mg.

REFERENCES