

Drugs affecting the autonomic nervous system

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Abstract

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

Keywords Autonomic nervous system; catecholamines; parasympathetic; sympathetic

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The autonomic nervous system (ANS) is divided on anatomical, physiological and pharmacological grounds into sympathetic (SNS) and parasympathetic (PNS) nervous systems (Tables 1 and 2). Both the SNS and PNS consist of pre- and post-ganglionic neurones. Pre-ganglionic fibres of the SNS arise from the thoracolumbar regions of the spinal cord, with pre-ganglionic fibres of the PNS arising from the craniosacral regions. Pre-ganglionic transmission in both the SNS and PNS is mediated via acetylcholine (ACh), acting at nicotinic acetylcholine receptors.

Post-ganglionic transmission in SNS neurones is primarily mediated by noradrenaline, acting via specific adrenergic receptors, except in sweat glands and the adrenal gland. Sweat gland post-ganglionic neurones release ACh. Pre-ganglionic fibres of the adrenal gland synapse directly with the adrenal medulla, stimulating the release of adrenaline from enterochromaffin cells. Adrenergic receptors are classified into three major types (α_1 , α_2 , and β), with further subtypes in each class. Two subtypes of β -receptor (β_1 and β_2) are well defined on functional, anatomical and pharmacological grounds and a third β -receptor subtype, β_3 , is found in adipocytes, skeletal and ventricular muscle and the vasculature. Dopaminergic (DA) receptors are now classified separately from adrenoceptors but are included here due to

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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

overlap in their actions and response to exogenous and endogenous catecholamines. There are five subtypes of DA receptors (D_1 – D_5) belonging to two subfamilies: D_1 -like and D_2 -like. D_1 -like receptors mediate vasodilatation in vascular smooth muscle of the renal, splanchnic, coronary and cerebral circulations; D_2 -like receptors are widespread in the central nervous system.

Post-ganglionic transmission in the PNS is mediated via acetylcholine, acting via muscarinic acetylcholine receptors of which there are five subtypes (M_1 – M_5).

Post-ganglionic 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).

Termination of neurotransmitter activity is brought about by a number of mechanisms. Acetylcholine is rapidly hydrolysed by the enzyme acetylcholinesterase to acetate and choline. Noradrenaline is removed from the synaptic junction by the *re-uptake* system, being returned to the sympathetic nerve that released it. It is subsequently metabolized intraneuronally by monoamine oxidase (MAO) enzymes. Circulating catecholamines and metabolized by the catechol-O-methyltransferase (COMT) enzyme system in the liver.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 autonomic nervous system (such as implantable carotid sinus stimulators or renal nerve ablation procedures) have been introduced for the treatment of drug-resistant hypertension; these are outside the scope of this article.

Sympathomimetics

Sympathomimetics mimic SNS stimulation by one of three mechanisms, acting directly on adrenoceptors (e.g. catecholamines, phenylephrine and methoxamine), indirectly by stimulating release of noradrenaline from nerve endings (e.g. amphetamine), or by combination of 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 catecholamines are based on a benzene ring structure with hydroxyl groups at the C3 and C4 positions. Substitutions in the amine

Adrenoceptors and acetylcholine receptors

Adrenoceptors				Acetylcholine receptors			
Receptor	Location	Second messenger	Selective antagonist e.g.	Receptor	Location	Second messenger	Selective antagonist e.g.
α_1	Smooth muscle, skeletal muscle, cardiac muscle, Liver	IP ₃ (G _q)	Prazosin, Doxazosin, Indoramin	Muscarinic M ₁	CNS, stomach, autonomic ganglia	IP ₃	Pirenzepine
α_2	Presynaptic sympathetic nerves, CNS, platelets	↓ cAMP (G _i)	Yohimbine, Idazoxan	M ₂	Heart, CNS, autonomic nerve endings	↓ cAMP (G _i)	None
β_1	Heart	cAMP (G _s)	Atenolol, Metoprolol, Bisoprolol, Esmolol	M ₃	CNS, salivary and mucous glands	IP ₃	None
β_2	Smooth muscle, skeletal muscle, cardiac muscle, liver	cAMP (G _s)		M ₄	CNS, cardiac muscle	↓ cAMP (G _i)	None
β_3	Fat, subcutaneous tissue	cAMP (G _s)		M ₅	?CNS	IP ₃	None
Nicotinic					Motor endplate	Ion channel ↑ Na ⁺ , ↑ Ca ⁺⁺ entry	
N ₁ (muscle receptors)					Autonomic ganglia	Ion channel ↑ Na ⁺ , ↑ Ca ⁺⁺ entry	
N ₂ (neuronal receptors)							

Stimulation of β_{1-3} receptors results in the activation of GTP binding G_s proteins, which in turn activates adenylate cyclase enzymes, generating cAMP to mediate the associated altered cell function. Stimulated α_2 , M₂ and M₄ receptors interact with G_i proteins to inhibit adenylate cyclase and hence reduce cAMP. Stimulation of α_1 , M₁ and M₃ receptors causes an interaction with the G_q protein. This leads to activation of membrane-bound phospholipase C, hydrolysing phosphatidylinositol biphosphate (PIP₂) to Inositol triphosphate (IP₃) and diacylglycerol (DAG). IP₃ binds to its receptor, opening Ca²⁺ channels. Nicotinic receptors are associated with non-selective ion channels that open up on their activation to effect changes.

Table 1

side-chain lead to the different hormones. Catecholamines have very short half-lives *in vivo* and are immediately inactivated in the gut by monoamine oxidase (MAO) enzymes. They are therefore usually administered parenterally, with doses being titrated to clinical effect. Choice of catecholamine 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) – is the principal catecholamine (80–90%) synthesized by the adrenal medulla and is a potent, non-selective sympathomimetic. It can administered intravenously (IV), intramuscularly (IM), topically or via nebulizer or tracheal tube. In non-emergency situations, adrenaline should be administered IM to reduce the risk of cardiac arrhythmias and intense vasoconstriction. In emergency situations (e.g. cardiac arrest, peri-arrest and anaphylaxis) the IV route is indicated.

The effects of adrenaline are dose-dependent. In low doses, β -effects predominate, leading to bronchodilation, and an increase in heart rate, cardiac output and myocardial oxygen consumption. Vasodilatation of skeletal muscle and splanchnic arterioles leads to a decrease in peripheral vascular resistance seen clinically as reduced diastolic pressure. At higher infusion

rates or bolus doses, α_1 -effects predominate, with vasoconstriction leading to an increase in systemic vascular resistance.

Adrenaline is included in a number of algorithms supported by the Resuscitation Council (UK), including those for cardiac arrest and anaphylaxis.² In cardiac arrest scenarios, adrenaline is administered at a dose of 1 mg (10 ml of 1:10,000 [0.1 mg/ml]) at alternating CPR cycles, with commencement depending on presenting rhythm. In anaphylaxis adrenaline is usually administered IM at a dose of 500 mcg (0.5 of 1:1000 [1 mg/ml] solution), although IV doses of 50–100 μ g (0.5–1 ml of 1:10,000 [0.1 mg/ml]) can alternatively be used. Adrenaline can be given by continuous infusion in shock states, administered at a dose range of 0.01–0.5 μ g/kg/minute.

Adrenaline is incorporated into local anaesthetic solutions, prolonging their duration of action by decreasing systemic adsorption (due to localized vasoconstriction). Adrenaline is also used as a topical vasoconstrictor to achieve local haemostasis and in the treatment of wide-angle glaucoma.

Noradrenaline (norepinephrine) – is synthesized in the adrenal medulla and post-ganglionic sympathetic nerve endings from the essential amino acid tyrosine as previously described. Noradrenaline acts primarily on α -receptors to cause intense arteriolar and venous vasoconstriction, usually accompanied by a reflex bradycardia. Noradrenaline is also an agonist at

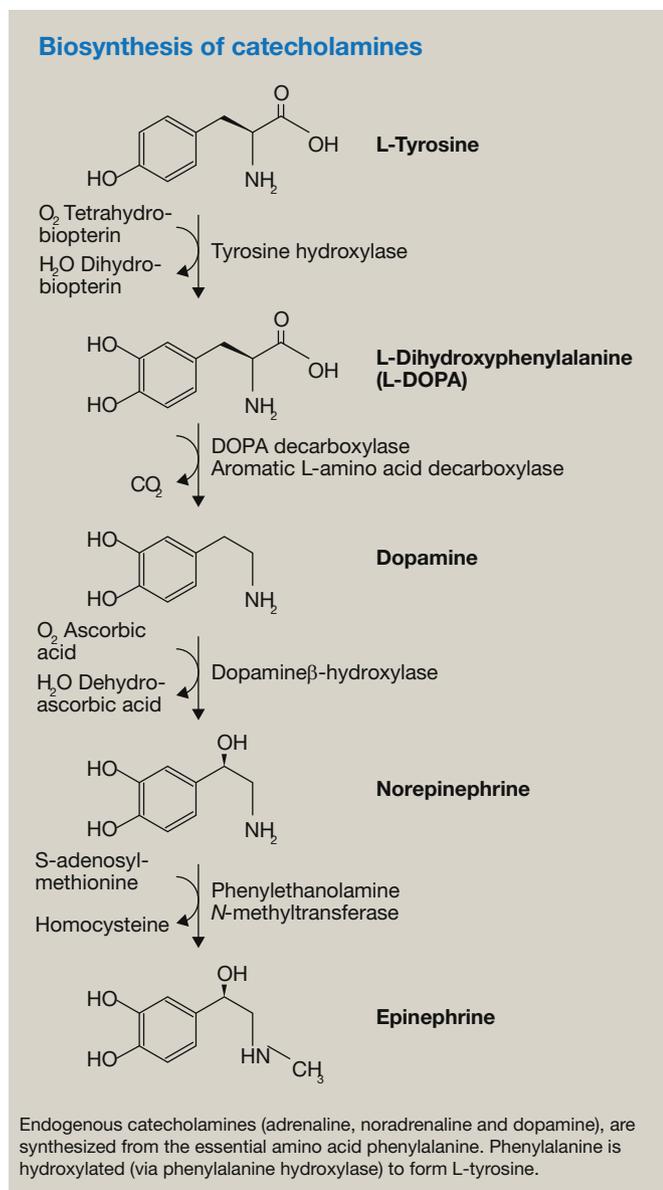


Figure 1

β -adrenoceptors and therefore falls in to the class of 'ino-constrictors', alongside the other endogenous catecholamines. Noradrenaline is primarily indicated in states of low systemic vascular resistance, as seen in sepsis and post-cardiac bypass. Noradrenaline increases systolic and diastolic pressures with an associated rise in pulmonary artery and central venous pressures. Cardiac output may fall (due to increased afterload), with an increase in myocardial oxygenation consumption. Noradrenaline is administered IV as an infusion through a central vein. The usual concentration is a solution of 100 $\mu\text{g}/\text{ml}$ administered at a dose of 0.05–1.5 $\mu\text{g}/\text{kg}/\text{minute}$.

Dopamine – is the natural precursor of adrenaline and noradrenaline (Figure 1). It directly stimulates α , β and dopaminergic receptors (D_1 and D_2), while also stimulating the 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 gland), with receptors also in the splanchnic and renal circulations.

The effects of dopamine are dose dependent. At doses of 1–5 $\mu\text{g}/\text{kg}/\text{minute}$, dopamine primarily stimulates D_1 receptors leading to renal and mesenteric vasodilatation, with an associated increase in blood flow. This leads to increased glomerular filtration, diuresis and natriuresis, though there is no evidence that dopamine in this range confers protection from renal dysfunction.³ Between 5 and 10 $\mu\text{g}/\text{kg}/\text{minute}$, β_1 effects predominate leading to increased inotropy, and cardiac output with lesser effects on heart rate. At doses above 15 $\mu\text{g}/\text{kg}/\text{minute}$, α -mediated effects predominate with an increase in systemic vascular resistance.

Dopamine has been used for the treatment of cardiogenic shock, refractory congestive cardiac failure and following cardiac surgery, although its use is declining (see Table 3).

Synthetic catecholamines:

Dobutamine – is a synthetic catecholamine similar in structure to dopamine. Dobutamine acts primarily at β_1 -receptors, with some activity at β_2 -receptors. Dobutamine increases cardiac contractility, heart rate and cardiac output (due to both an increase in contractility and mild decrease in afterload). It also increases conduction through the AV node and should be used with caution in patients with atrial fibrillation. Dobutamine is administered as an IV infusion, the usual dose being 0.5–40 $\mu\text{g}/\text{kg}/\text{minute}$.

Dopexamine – is a synthetic dopamine analogue that stimulates β_2 and D_1 receptors and may also inhibit neuronal noradrenaline reuptake. It has minimal effect on D_2 receptors. The combination of β_2 and D_1 stimulation leads to increased chronotropy and inotropy of the heart, alongside vasodilation and a decrease in systemic vascular resistance, seen particularly in the mesenteric, skeletal and renal vascular beds. Dopexamine is used in the treatment of acute primary cardiac failure and low cardiac output states. The dose range of dopexamine is 0.5–6 $\mu\text{g}/\text{kg}/\text{minute}$.

Isoprenaline – is a β -adrenoceptor agonist. It has been used for the temporary treatment of bradyarrhythmias and atrioventricular block owing to its effects primarily on β_1 receptors. This leads to an increase in automaticity and heart rate (arrhythmias are common). β_2 -Effects produce bronchodilation, vasodilatation and a decrease in systemic vascular resistance. Increased inotropy and decreased afterload lead to an increase in cardiac output. It is now only available in the UK from special-order manufacturer or specialist importing companies.

Non-catecholamine sympathomimetic drugs

Ephedrine is a naturally occurring sympathomimetic amine that acts both directly (stimulating both α and β 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 bronchodilation 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 COMT and MAO. Intravenous doses range from 3 to 30 mg. Owing to its indirect actions, tachyphylaxis can develop due to depletion of noradrenaline from nerve

The effects of sympathetic and parasympathetic nervous systems on effector organs

Organ	Sympathetic		Parasympathetic	
	Receptor	Effect	Receptor	Effect
Heart	β_1, β_2, α and D_1	↑ Heart rate, force of contraction, excitability	M_2	↓ Heart rate
	α_1	Force of contraction		↓ Force of contraction
Arteries	α_1, α_2	Vasoconstriction	M	Vasodilatation in skeletal muscle, skin, pulmonary and coronary circulations
	β_1	Coronary vasodilatation		
	β_2	Skeletal muscle vasodilatation		
	D_1, β_2	Splanchnic, renal vasodilatation		
Veins	α_1, α_2	Vasoconstriction		
	β_2	Vasodilatation		
Lungs	α_1	Bronchoconstriction	M_3	Bronchoconstriction
	β_2	Bronchodilatation, ↓ secretions		↑ Secretions
Kidneys	β	Renin secretion		
Liver	β_2 and α	Glycogenolysis Gluconeogenesis	M	Glycogen synthesis
Bladder	β_2 and α	Detrusor relaxation Sphincter contraction	M	Detrusor contraction Sphincter relaxation
Uterus	α_1	Myometrial contraction		
	β_2	Myometrial relaxation		
Eye	α_1	Mydriasis, ciliary muscle relaxation	M	Miosis, ciliary muscle contraction

The five different muscarinic receptor subtypes (M_{1-5}) have been classified using selective radioactively-labelled agonist and antagonist substances.⁵ Note that in some cases the receptor subtype is unknown.

Table 2

The effects of endogenous and synthetic sympathomimetics including receptor type

	Drug	Receptors	Effects
Endogenous	Adrenaline	$\alpha = \beta$	↑ CO, coronary blood flow bronchodilator ↑ Splanchnic blood flow ↓ Intestinal tone
	Noradrenaline	$\alpha > \beta$	↑ SVR, coronary vasodilatation, reflex bradycardia ↓ Hepatic, splanchnic blood flow bronchodilation
	Dopamine	$D_1 > \beta > \alpha$ ↑ Dose	↑ Cardiac output and coronary blood flow ↑ SVR at high doses splanchnic vasodilatation
Synthetic	Dobutamine	$\beta_{1\&2}$	↑ Contractility, HR ↓ LVEDP, SVR ↑ Urine output
	Dopexamine	D_1, D_2 , inhibits NA reuptake β_2 agonist	↑ Cardiac output afterload ↓ bronchodilatation ↑ Mesenteric blood flow
	Isoprenaline	β	Positive inotrope, chronotrope ↑ SBP, ↓ DBP Bronchodilator CNS stimulant

Endogenous and synthetic catecholamines have different effects based on the receptor type that they stimulate which dictates their use. CNS, central nervous system; DBP, diastolic blood pressure; LVEDP, left ventricular end-diastolic pressure; NA, noradrenaline; SBP, systolic blood pressure; SVR, systemic vascular resistance.

Table 3

terminals. Ephedrine easily crosses blood brain barrier and can be 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 foetal metabolic rate and metabolic acidosis, so has been superseded by phenylephrine in obstetric patients.⁴

Phenylephrine is a direct-acting α_1 agonist, causing vasoconstriction and a rapid rise in blood pressures. 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 GI tract and the bioavailability of phenylephrine is approximately 38%. Phenylephrine has largely replaced ephedrine as the vasopressor of choice in obstetric anaesthesia. Phenylephrine can be administered as a bolus of 50–100 μg IV or used as an infusion. Effects occur within 1 minute with a duration of up to 45 minutes after bolus injection. Phenylephrine has no inotropic or chronotropic effects directly but should be used with caution as marked reflex bradycardia can occur.

Metaraminol is a direct- and indirect-acting α and β -agonist. Acting mainly via α_1 receptors, its main actions are to increase blood pressure via an increase in systemic vascular resistance. Pulmonary vascular resistance is also increased leading to pulmonary arterial hypertension. The dose range is 0.5–2 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.

α_2 -Adrenoceptor agonists

Clonidine acts at central and peripheral α_2 receptors as a partial agonist (some α_1 activity $\alpha_2:\alpha_1 >200:1$) and as a full agonist at central imidazoline receptors. Transient hypertension and bradycardia can occur after IV injection through stimulation of vascular α_2 receptors followed by centrally mediated hypotension. Bolus doses of 2–3 $\mu\text{g}/\text{kg}$ attenuate sympathetic responses during anaesthesia, while 1–2 $\mu\text{g}/\text{kg}$ neuraxially increases the potency and duration of analgesic block. Clonidine is absorbed well orally with peak plasma levels at 60–90 minutes. Clonidine can be used orally to treat hypertension and can be given as an intravenous infusion to provide sedation on the critical care unit.

Dexmedetomidine is a full agonist at central and peripheral α_2 receptors ($\alpha_2:\alpha_1 >1600:1$), with a selectivity eightfold to tenfold greater than clonidine for α_2 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 can be used as a single-agent sedative in intensive care, administered as an infusion in the dose range of 0.2–1.4 $\mu\text{g}/\text{kg}/\text{hour}$.

Sympatholytic drugs

α -Adrenoceptor antagonists:

Non-selective α antagonists – *Phentolamine* and *phenoxylbenzamine* are used in the management of hypertensive crises and pheochromocytoma.

Phentolamine is a competitive non-selective α -blocker, predominantly acting at α_1 -adrenoceptors (three times the affinity than for α_2). It can be administered as an intravenous bolus at a dose of 1–5 mg repeated as necessary to effector as an infusion at a rate of 0.1–0.2 mg/minute. It has an onset of 1–2 minutes and duration of action between 5 and 20 minutes.

Phenoxybenzamine is a non-competitive irreversible α -blocker with a high affinity for α_1 . It is administered orally, starting at a dose of 10 mg and increased as required; the usual maintenance dose is 1–2 mg kg^{-1} daily in two divided doses. Onset time is several hours with a duration of action lasting up to 3 days owing to its prolonged elimination, covalent binding and the need for new α -adrenoceptors to be synthesized.

Both phentolamine and phenoxybenzamine can produce postural hypotension with reflex tachycardia. Abdominal side-effects can also be present including cramps and diarrhoea.

Selective α_1 antagonists – Drugs that selectively block α_1 -adrenoceptors are predominantly used for the symptomatic treatment of benign prostatic hyperplasia as they cause relaxation of prostatic smooth muscle and increase urinary flow. Doxazosin, indoramin and prazosin are also licenced for the treatment of hypertension, though the latter two drugs have largely been superseded for this indication. All can cause postural hypotension and a condition associated with cataract surgery known as ‘floppy iris syndrome’.

Doxazosin is a selective α_1 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. The usual dose is 2–4 mg (maximum 16 mg) daily.

Tamsulosin predominantly blocks prostatic α_{1a} receptors as opposed to vascular α_{1b} 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.

β -Adrenoceptor antagonists: β -Blockers are classified according to their receptor selectivity (β_1 or β_2). All β -blockers are competitive antagonists and bind avidly to their specific receptors. β -Blockers decrease cardiac contractility and automaticity, and increase refractory times at the 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 airway 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 some antagonize other receptors.

Non-selective β -antagonists – *Propranolol* is a non-selective β -blocker that also exhibits a membrane stabilizing effect through its action on Na^+ channels (although not in clinically significant doses). It has no sympathomimetic actions, is highly lipid-soluble and crosses the blood brain barrier. Propranolol is used to treat the sympathetic manifestations of anxiety, for thyrotoxicosis, portal hypertension, hypertrophic obstructive cardiomyopathy, migraine but has been superseded in the treatment of hypertension and angina. It is administered orally (30–320 mg/day) in 2–3 divided doses, or IV 1–10 mg titrated to response.

Carvedilol and *labetalol* are non-selective β -blockers that also antagonize α_1 -receptors. Labetalol is primarily used in the

treatment of hypertensive crises particularly pregnancy-induced hypertension and pre-eclampsia. The ratio of β to α activity varies with route of administration (7:1 when administered IV). 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). Adverse effects include insomnia, drowsiness and rarely respiratory distress.

Selective β_1 blockers – *Atenolol* is a relatively cardioselective (β_1) beta blocker that can be administered orally (50–100 mg/day) or IV (2.5–10 mg, max 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 possesses 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 β_1 receptors compared to atenolol and propranolol. 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 β_1 -selective blocker used in the treatment of supraventricular tachyarrhythmias (atrial flutter and fibrillation) and perioperative hypertension. Esmolol is metabolized by erythrocyte esterases to produce methanol and a weaker active metabolite. It is administered IV as bolus (0.5–2.0 mg/kg) or an infusion (25–500 μ g/kg/minute) with clinical effects within 2 minutes and duration of action of approximately 10 minutes.

Drugs acting on the parasympathetic nervous system

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 including increased heart rate, decreased bladder tone, decreased salivary secretions, increased intraocular pressure and mydriasis. Atropine is administered IV in a dose of 0.6–3.0 mg to counter intense vagal stimulation (the dose in children is 20 μ g/kg). At very low doses there is a paradoxical bradycardia thought to be mediated by M_2 receptor antagonism centrally in the CNS (Bezold–Jarisch effect). The therapeutic dose effects are mediated by M_3 receptors, while 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 antisialogogue 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 antisialogogue. 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. ◆

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