Drugs affecting the autonomic nervous system

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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 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) 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 (α, β, and δ) 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 adrenergic receptors 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, splanchnic, 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-M₅). 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 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) — adrenaline is the principal catecholamine (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
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. 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, vasodilatation 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, thereby increasing glomerular filtration, urine production and sodium excretion. Between 5 and 10 μg/kg/minute, β1 effects predominate causing an increase in contractility, heart 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
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 β₁ receptors but also has some activity at β₂ and to a lesser degree at α receptors. It has no effect on D 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 (β₁). There is also a degree of afterload reduction mediated through β₂ 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 μg/kg/minute.

**Dopexamine** — dopexamine is a synthetic dopamine analogue that stimulates β₂, D₁ and D₂ receptors and also inhibits neuronal noradrenaline reuptake. β₂ 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 μg/kg/minute up to a maximum of 6 μg/kg/minute.

**Isoprenaline** — isoprenaline acts solely on β receptors. Effects on β₁ receptors cause an increase in automaticity and heart rate (arrhythmias are common); β₂ 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 β₂ effects are bronchodilatation and mast cell stabilization but isoprenaline has been superseded in the treatment of asthma by specific β₂ agonists with fewer adverse cardiac effects. It may be used for the temporary treatment of bradyarrhythmias 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 μg/minute.

Non-catecholamine sympathomimetic drugs

**Ephedrine** — ephedrine is a naturally occurring sympathomimetic amine which 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 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.
quickly metabolized by COMT and MAO. Diffusion into circulation. Catecholamines that enter the circulation are metabolized catecholamines are secreted by the kidneys in the urine. 3. mainly in the liver, kidneys and gut but do occur in many other tissues. The metabolism of endogenous catecholamines are monoamine oxidase (MAO) and catechol-O-methyl transferase (COMT). These are present primarily in the liver, kidneys and gut but do occur in many other tissues. The metabolized catecholamines are secreted by the kidneys in the urine. 3. Diffusion into circulation. Catecholamines that enter the circulation are quickly metabolized by COMT and MAO.

Figure 1 Stimulation of preganglionic nicotinic receptors at the adrenal medulla causes the release of adrenaline into the circulation. Adrenaline and the other endogenous catecholamines (noradrenaline and dopamine) are synthesized from the essential acid phenylalanine, which is hydroxylated to produce L-Tyrosine. The core structure for the catecholamines comprises a catechol ring with an amine side chain (substitutions in which create the different hormones). After interaction with the adrenergic receptor, the action of catecholamines is terminated in one of three ways: 1. Reuptake 1 and 2. Reuptake 1 is an active process which is dependent on adenosine triphosphate (ATP) and magnesium. The norepinephrine is taken back into the presynaptic nerve terminal and stored in cytoplasmic vesicles ready to be used again. Reuptake 2 describes norepinephrine being taken back into the postsynaptic neuron (predominantly in smooth muscle cells). 2. Enzymatic degradation. The two enzymes responsible for the metabolism of endogenous catecholamines are monoamine oxidase (MAO) and catechol-O-methyl transferase (COMT). These are present primarily in the liver, kidneys and gut but do occur in many other tissues. The metabolized catecholamines are secreted by the kidneys in the urine. 3. Diffusion into circulation. Catecholamines that enter the circulation are quickly metabolized by COMT and MAO.

### Effects of endogenous and synthetic sympathomimetics including receptor type

<table>
<thead>
<tr>
<th>Drug</th>
<th>Receptors</th>
<th>Effects</th>
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<tbody>
<tr>
<td>Endogenous</td>
<td>Adrenaline</td>
<td>( \alpha = \beta )</td>
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<tr>
<td></td>
<td>Noradrenaline ( \alpha &gt; \beta )</td>
<td>( \uparrow ) Cardiac output and coronary blood flow</td>
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<tr>
<td>Dopamine</td>
<td>( D_1 &gt; \beta &gt; \alpha )</td>
<td>( \uparrow ) Cardiac output and coronary blood flow</td>
</tr>
<tr>
<td>Dopexamine</td>
<td>( D_1, D_2 )</td>
<td>( \uparrow ) Urine output</td>
</tr>
<tr>
<td>Isoprenaline</td>
<td>( \beta )</td>
<td>( \uparrow ) Positive inotrope</td>
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<tr>
<td>Synthetic</td>
<td>Dobutamine</td>
<td>( \beta_{1.2} )</td>
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<tr>
<td></td>
<td>Dopamine</td>
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<td>Isoprenaline</td>
<td>( \beta )</td>
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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

Doses vary from 3 to 30 mg IV but above this tachyphylaxis develops due to depletion of noradrenaline from nerve terminals. Ephedrine easily crosses 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. 3

**Phenylephrine** — phenylephrine is a selective \( \alpha_1 \) 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 \( \mu \)g IV or used 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, vasodilatation and hypotension. Tachyphylaxis is problematic and they have been superseded by newer more selective drugs.

**α receptor antagonists**

*Non-selective α antagonists: phenolamine, 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 α₁b receptors rather than vascular α₁a 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 ‘flloppy 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 adrenoreceptor 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.

**Hyoscyamine** 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 antimalologue than atropine and causes problems in the elderly, as it crosses the blood–brain barrier causing confusion, sedation and ataxia (central anticholinergic syndrome). Hyoscyamine is used as an antietemic, 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 antimalologue. 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**