PHARMACOLOGY OF VASOPRESSORS AND INOTROPES

Dr Karen Gilmore, Frenchay Hospital, Bristol, UK & Christine Nanyanzi, Gihundwe Hospital, Rwanda.

A "vasopressor" causes vasoconstriction and an "inotrope" increases the force of cardiac contraction. Vasopressors and inotropes work via the Autonomic Nervous System.

Neurotransmission at postganglionic receptors. The postganglionic receptors of the Parasympathetic Nervous System PNS are termed muscarinic, and acetylcholine (Ach) is the neurotransmitter. The equivalent receptors in the Sympathetic Nervous System (SNS) are noradrenergic receptors and noradrenaline (Norad) is the endogenous (naturally occurring) neurotransmitter (table 1).

These noradrenergic receptors are further subdivided, the subdivisions relevant to this article are Alpha1 (α1), Beta1 (β1), Beta2 (β2) and Dopamine (D). The main actions of each receptor subtype are as shown in table 2.

VASOPRESSORS AND INOTROPES

This group of drugs is useful for resuscitation of seriously ill patients, and for the treatment of hypotension in theatre. All of these drugs act directly or indirectly on the SNS, but the effect of each varies according to which sympathetic receptor the drug has greatest affinity for. The duration of action also varies. **Direct acting drugs** act by stimulating the SNS receptor whereas **indirect acting drugs** cause the release of noradrenaline from the receptor which produces the effect. Some drugs have a mixed effect.

ADRENALINE (EPINEPHRINE)

Adrenaline acts on α1, β1 and β2 receptors. It is said to prepare the body for a "fight or flight" response.

Table 1

	Preganglionic receptor type (and neurotransmitter)	**Post ganglionic receptor type (and neurotransmitter)**
PNS	Nicotinic (Ach)	Muscarinic (Ach)
SNS	Nicotinic (Ach)	Noradrenergic (Norad)

Actions

CVS: Increased heart rate and force of contraction produce an increase in cardiac output. Systolic blood pressure (SBP) rises, but with low doses diastolic blood pressure (DBP) may fall due to vasodilation and increased blood flow through skeletal muscle beds (β2). At higher doses the vasoconstrictor effects of α1 stimulation become more apparent, causing the cool pale extremities of a frightened person.

RS: Bronchial smooth muscle is relaxed resulting in bronchodilation (β2).

Other: Adrenaline mobilises glucose from glycogen and raises blood sugar. Pupillary dilation (mydriasis) occurs.

Side effects Ventricular arrhythmias, hypertension. Care with halothane anaesthesia as arrhythmias may occur.

Preparation 1:1000 i.e. 1mg in 1 ml.
1:10,000 i.e. 1mg in 10ml

Indications and doses

Cardiac Arrest - see page 21

Anaphylactic shock - 1:10,000 adrenaline given iv in 1 ml doses until effective. If no iv access available then 0.5ml of 1:1,000 im.

Additive to local anaesthetic - add adrenaline to local anaesthetic to make a concentration of 1:200,000 - see page 50

Acute severe asthma attack unresponsive to normal treatment may require infusions of adrenaline, though 0.5ml of 1:1000 s/c may be used.

Septic shock - require infusions of adrenaline

Length of action Short, few minutes only with intravenous bolus.

EPHEDRINE

Ephedrine acts directly on β1 and β2 receptors, and indirectly on α1 receptors by causing noradrenaline release.

Action It causes a rise in blood pressure and heart rate, and some bronchodilation.

Side effects May cause tachycardia and hypertension. Possible arrhythmias if used with halothane.

Preparation 3% or 5% solution: 1 ml ampoules.

Indications Low blood pressure due to vasodilation e.g. following spinal or epidural anaesthesia and drug overdoses. Best vasopressor to use in pregnancy as it does not reduce placental blood flow.

Dose 3-10 mg boluses iv, repeat until effective. Maximum dose is 60mg.

Length of action 5-15 minutes, repeated doses less effective (i.e. it demonstrates tachyphylaxis).

METHOXAMINE

Methoxamine acts on α1 receptors.

Actions Increases blood pressure. There may be a reflex decrease in heart rate, and therefore it is good for hypotension with tachycardia. Useful during spinal anaesthesia.

Table 2

α1	Peripheral arteriolar vasoconstriction
β1	Cardiac increased heart rate and force of contraction.
β2	Bronchial smooth muscle dilation.
	Vasodilation in skeletal muscle. Also some cardiac effects.
D	Increased renal blood flow

For a full explanation of receptors and their actions refer to Update in Anaesthesia 1995:5

Side effects May produce bradycardia

Dose 2-4mg boluses IV, repeated as necessary.

METARAMINOL

Acts directly on α1 receptors and also causes noradrenaline and adrenaline release.

Actions Increases blood pressure and cardiac output. Less likely to cause a reflex bradycardia than methoxamine or phenylephrine.

Dose - 1mg boluses iv, 2-10mg s/c or im, by infusion at 1-20mg/hr.

PHENYLEPHRINE

Acts directly on α1 receptors,

Action Hypertension and a reflex decrease in heart rate.

Dose 2-5mg im or sc, 0.1-0.5mg iv, by infusion 20-50mcg/min.

INOTROPES GIVEN BY INFUSION

Adrenaline is the most commonly available inotrope, and in many cases the most appropriate drug to maintain blood pressure. When other inotropes are available, some may offer advantages in certain situations. The inotropes listed below are only given by infusion unless a bolus dose is stated. They are mostly very short acting, their effects lasting from a few seconds to one or two minutes and should be given via a central line (except for aminophylline and salbutamol) via an infusion controller. The patient must be closely monitored, particularly the ECG and blood pressure. Tachycardia, arrhythmias, and hypertension or hypotension are side effects of these drugs. Although called inotropes some of these drugs also have vasoconstrictor properties.

NORADRENALINE

Acts mainly on α1 receptors with few effects on β receptors.

Actions Increases blood pressure by vasoconstriction. Less likely to cause tachycardia than adrenaline.

Indications Septic shock where peripheral vasodilation may be causing hypotension.

Cautions Acts by increasing afterload and therefore not appropriate for use in patients in cardiogenic shock. Blood supply to kidneys and peripheries may be reduced.

Dose - 1-30mcg/min

- Add 4mg to 250ml 0.9% NaCl or 5% dextrose to give 16mcg/ml. Run at 0-112ml/hr

DOPAMINE

Acts on D, β1, β2 and α1 receptors, depending on the dose administered.

Actions Dose dependent. It used to be popular to increase urine output via its effect on the D receptors in the kidney. However, less commonly used for this purpose as it does not prevent renal failure.

Indications Hypotension.

Dose *1-2mcg/kg/min* - acts on D receptors usually increasing urine output

2-10mcg/kg/min - also acts on β receptors to increase cardiac output

>10mcg/kg/min - additionally has effects on α1 receptors to vasoconstrict.

- Add 3mg/kg (body weight) to 50mls 0.9%NaCl or 5% glucose
- 1ml/hr = 1mcg/kg/min

DOBUTAMINE

Acts on β1 and β2, with minimal action on α1 receptors.

Actions It increases cardiac output and reduces afterload (β2effects on skeletal muscle).

Indications Cardiogenic shock.

Dose 2-30mcg/kg/min

- Add 3mg/kg to 50mls 0.9%NaCl or 5% glucose
- 1ml/hr = 1mcg/kg/min

DOPEXAMINE

Acts on β2 and D receptors.

Actions It increases cardiac output and reduces afterload. Increases blood supply to the kidneys and possibly also the gastrointestinal tract.

Dose 0.5-6mcg/kg/min

SALBUTAMOL
Acts on β2 receptors

Actions Relaxes bronchial smooth muscle i.e. bronchodilation, may increase heart rate

Indications Severe acute asthma.

Dose By infusion 5-20mcg/min.Can also be given in bolus form iv in the initial treatment of an attack at a dose of 5mcg/kg over several minutes.

ISOPRENALINE
Acts on β1 and β2 receptors

Actions Main action is increased heart rate. Also increased force of contraction, and bronchodilation.

Indications Complete heart block, overdose of beta blocker or severe bradycardia unresponsive to atropine. Can be used to treat asthma, but less suitable than drugs that act only on β2 receptors e.g. salbutamol

Dose 0.02-0.2mcg/kg/min by infusion
5-20mcg bolus iv

PHOSPHODIESTERASE INHIBITORS (e.g. AMINOPHYLLINE, ENOXIMONE)
Prevent breakdown of cAMP by enzyme phosphodiesterase: this produces effects at β1 and β2 receptors.

Actions Inodilation i.e. increased rate and force of contraction, vasodilation in skeletal muscle. Also bronchodilation.

Indications Aminophylline: asthma, cardiac failure.
Enoximone: cardiac failure in patients failing to respond to dobutamine

CLINICAL CASE STUDY – USE OF VASOPRESSORS
Lower segment Caesarean section (LSCS) under spinal anaesthesia
A patient is scheduled for LSCS under spinal anaesthesia. An iv ifusion is set up and 1000 mls of Hartmanns run in whilst the spinal is performed. The patient is placed supine with a 15-degree left-lateral tilt to minimise aortocaval compression (i.e. pressure from the uterus on the inferior vena cava reducing venous return to the heart).

Despite good positioning and iv fluids, hypotension is very likely at this stage because of vasodilation due to the spinal. The patient should be given ephedrine in boluses of 6-9mg, which may need to be repeated several times. Alternatively, 30-60mg of ephedrine can be added to the intravenous infusion, and the rate titrated according to the BP. The SBP should be maintained above 100mmHg. (A hazard of adding ephedrine to the infusion is that the anaesthetist may forget to reduce the rate of infusion when the BP has returned to normal, and the patient may become dangerously hypertensive.)

Once the baby has been delivered aortocaval compression is no longer a problem, and further ephedrine is not usually required. If hypotension persists, ensure that hypovolaemia is not the cause. Intravenous fluids should be given to restore blood volume, rather than vasopressors. Ephedrine is the best vasopressor for LSCS because it has fewest effects on placental blood supply. If ephedrine is not available another vasopressor should be used. Alternatively small doses of adrenaline (20-50mcg) can be given, in a dilute preparation.

Summary
The common causes of hypotension during LSCS under spinal anaesthesia are:

- Vasodilation - treat with fluids and ephedrine
- Aortocaval compression – tilt patient 15 degrees to left
- Bleeding – replace blood loss with intravenous fluids