

Q12 Outline the pharmacology of noradrenaline (Sept 2009)

Noradrenaline is the major endogenous catecholamine released from sympathetic nerve terminals. It differs from adrenaline only by lacking the methyl substitution in the amino group. It also constitutes 10-20% of the catecholamine substance of the adrenal medulla. It is used for maintenance of haemodynamic parameters in critical care settings.

PHARMACEUTICAL

Endogenous noradrenaline is synthesised from the hydroxylation of dopamine. Synthetic noradrenaline is presented as an injectable solution only.

PHARMACODYNAMICS

Mechanism – the effects of noradrenaline are mainly due to alpha 1 receptor agonism (Gq protein coupled receptors), causing an increase in intracellular calcium and hence peripheral vasoconstriction. It has some effect on beta receptors as well (mainly beta 1). Its overall effects are an increase in SVR, systolic and diastolic blood pressure and myocardial oxygen consumption. Coronary flow is usually increased due to the increased MAP as well as indirectly induced coronary dilatation. There may be a reflex bradycardia and a fall in cardiac output. There may be a fall in renal and hepatic blood flow due to vasoconstriction (although this may be somewhat offset by the improvement in MAP). Blood flow to the pregnant uterus is also reduced and may result in fetal bradycardia.

Side effects – In excess it produces hypertension, bradycardia, headache and skin necrosis due to excessive peripheral vasoconstriction. It tends to cause fewer metabolic side effects (eg hyperglycaemia) than adrenaline. Extravasation can cause tissue necrosis.

PHARMACOKINETICS

ADMINISTRATION

Route - IV (ideally central line only due to risk of tissue necrosis)

Bioavailability – 100%

Dose - start at 0.01mcg/kg/min and titrate to effect

Time to onset of action - seconds

DISTRIBUTION

Does not cross the BBB

METABOLISM

Uptake 1 – the main mechanism of inactivation. Describes the active uptake of Nad back into the nerve terminal where it is metabolized by MAO (monoamine oxidase) or recycled

Uptake 2 – describes the diffusion away from the nerve terminal into the circulation, where it is metabolized by COMT (catechol-O-methyltransferase) to the inactive vanillylmandelic acid and normetadrenaline)

Up to 25% taken up in the pulmonary circulation

ELIMINATION

Half life 2 min

Excreted in urine (mostly inactive)