# METHYLDOPA / CENTRAL ALPHA$_2$ AGONIST

Methyldopa is a centrally acting antihypertensive agent that exerts its antihypertensive action via an active metabolite. Methyldopa's significant adverse effects currently limit its use in the U.S. to treatment of hypertension in pregnancy, where it has a record for safety.

## PHARMACEUTICAL ASPECTS

It is available as an oral formulation in Australia in 250mg tablets.

## PHARMACODYNAMIC ASPECTS

Its metabolite produces a clonidine like alpha2 agonist effect in cardiovascular control centres that results in reduced sympathetic outflow. The metabolite also acts as a false neurotransmitter reducing peripheral SNS effects by reducing noradrenaline synthesis. It is primarily used to dpress overall SNS activity (HR, BP and TPR) but can also cause sedation, psychosis and depression.

## PHARMACOKINETIC ASPECTS

| | |
|---|---|
| ABSORPTION | bioavailabilty absorded by an amino acid transporter (% ?)<br>routes of administration oral<br>doses 125-250mg BD titrated<br>onset of action 3-6 hours, duration 24 hours (this is becuase of the prolonged process in substituting for noradrenaline in peripheral sites) |
| DISTRIBUTION | protien binding <15% |
| METABOLISM | mechanism Intestinal and hepatic |
| ELIMINATION | half life 75-80 minutes (extended in renal failure)<br>excretion Urine (85% as metabolites) within 24 hours |

## MAJOR ISSUES OR SIDE EFFECTS

Sedation, decreased mental acuity and depression may occur. Dry mouth is also a problem. A small percentage of patients develop hepatotoxicity or a haemolytic anaemia.

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# MINOXIDIL/DIRECT VASODILATOR (?K ACTIVATOR)

Minoxidil is a direct vasodilator whose mechanism of action is poorly understood. It is described by Goodman as a potassium channel actiivator but this is contradicted in other texts. It is used primarily in sever refractory hypertension in combination with other antihypertensives.

## PHARMACEUTICAL ASPECTS

It is available in 10mg tablets

## PHARMACODYNAMIC ASPECTS

Similar to hydralazine in that different textbooks identify different mechanisms for this drug which indicate the poor understanding. The effects are arteriole vasodilation with preserved venous tone, and minimal effect on epicardial vasculature. There is a reflex increase in HR, CO and activation of the RAAS leading to peripheral oedema. Interestingly it is associated with increased hair production and is used topically to treat baldness.

## PHARMACOKINETIC ASPECTS

ABSORPTION
- bioavailabilty up to 90%
- routes of administration oral
- doses 10-40mg PO daily
- onset / duration ~30 minutes / up to 5 days due to avid smooth muscle binding

DISTRIBUTION
- protien binding None

METABOLISM
- mechanism Hepatic primarily via glucuronidation

ELIMINATION
- half life 4 hours
- excretion Urine (12% as unchanged drug)

## MAJOR ISSUES OR SIDE EFFECTS

The activation of the RAAS and the increase in HR and CO make this drug less efficacious. Because of this reason it is almost always given in combination with a thiazide or betablocker. It is contraindicated in phaechromocytoma and may precipitate pericardial effusion and worsen angina.

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# PHENOXYBENZAMINE / ALPHA BLOCKER

Phenoxybenzamine is a long acting non selective alpha blocker. It has a high affinity for alpha1 adrensoceptors. It is used in the treatment of phaeochromocytoma.

## PHARMACEUTICAL ASPECTS

It is presented a capsules containing 10mg and as a clear faintly straw coloured solution for IV injection containing 100mg/2ml.

## PHARMACODYNAMIC ASPECTS

Importantly it forms covalent bonds with alpha-adrenoceptors, so that the effects of single doses can last for at least several days. The restoration of normal responsiveness to alpha-adrenoceptor agonists is dependent on the synthesis of new receptors. It causes peripheral vasodilation, relaxes the urethra and increases opening of the bladder

## PHARMACOKINETIC ASPECTS

| | |
|---|---|
| ABSORPTION | bioavailabilty is 20-30% in oral form<br>routes of administration oral or IV<br>doses 10-20mg BD, uptitrate to control BP |
| DISTRIBUTION | volume of distribution not known<br>protien binding not known<br>lipid solubility not known |
| METABOLISM | mechanism not known |
| ELIMINATION | half life IV is 24 hours<br>excretion not known |

## MAJOR ISSUES OR SIDE EFFECTS

Orthostatic hypotension, syncope and vertigo as per other alpha blockers.

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# TIROFIBAN / GLYCOPROTIEN IIb/IIIa ANTAGONIST

Tirofiban binds to the glycoprotien IIb/IIIa receptor on the surface of platelets. It has a similar action to the monoclonal antibody abciximab. It is used in patients with non stable angina and NSTEMI in high risk patients.

## PHARMACEUTICAL ASPECTS

It is presented for injection in 0.25mg/ml in 50ml vials. Its trade name is aggrastat. It is usually given with low dose aspirin and heparin infusion. All markers of coagulation should be checked within six hours of commencing treatment, and then daily.

## PHARMACODYNAMIC ASPECTS

Tirofiban and abciximab act by inhibiting the platelet glycoprotien IIb/IIIa receptor and as such they block the final common pathway of platelet aggregation. They do not block platelet adhesion, secretion of platelet products, inflammatory effects or thrombin activation.

## PHARMACOKINETIC ASPECTS

| | |
|---|---|
| ABSORPTION | bioavailabilty<br>routes of administration<br>doses<br>onset / duration more rapid offset than abciximab and other agents. |
| DISTRIBUTION | volume of distribution<br>protien binding |
| METABOLISM | mechanism |
| ELIMINATION | half life<br>excretion 65% renal and 25% faecal clearance |

## MAJOR ISSUES OR SIDE EFFECTS

Requires dose adjustment in renal failure with creatinine clearance <30ml/min. Side effects relate to haemorrhage, although spontaneous haemorrhage is uncommon. Reversal is problematic and platelet infusion is recommended if there is uncontrolled bleeding.

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