



# Methyldopa

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## Introduction

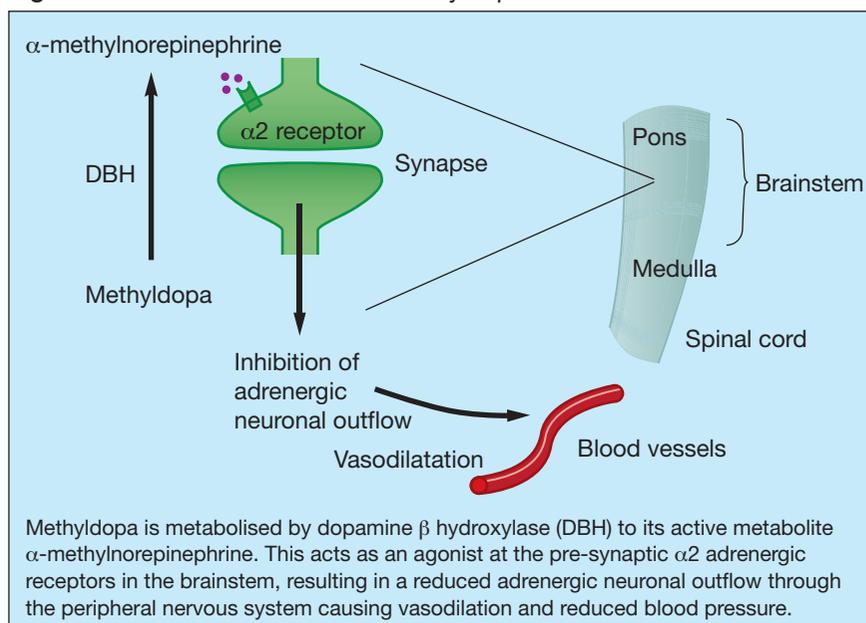
Methyldopa ( $\alpha$ -methyl-3, 4-dihydroxy-L-phenylalanine) was synthesised and shown to be a potent inhibitor of renocortical DOPA decarboxylase by Sourkes in 1954. Stein *et al.* presented the chemical characteristics of methyldopa in 1955 and in 1960 Sjoerdsma *et al.* demonstrated its antihypertensive action in humans. In the 1970s, methyldopa was considered an effective antihypertensive agent, especially in the elderly, patients with renal insufficiency, and pregnancy. The side effect profile of methyldopa, along with the launch of newer antihypertensives, resulted in methyldopa being removed from first line treatment in hypertension in the developed countries. Despite these changes, methyldopa remains a safe alternative for treatment of hypertension in the developing countries due to its low cost.

## Pharmacology

Methyldopa is an analogue of DOPA (3, 4 dihydroxyphenylalanine). The antihypertensive effect of methyldopa is probably through its active metabolite,  $\alpha$ -methylnorepinephrine. This acts as an agonist at presynaptic  $\alpha_2$  adrenergic receptors in the brainstem and results in the inhibition of adrenergic neuronal outflow. The attenuation of norepinephrine release in the brainstem reduces the output of vasoconstrictor adrenergic signals to the peripheral sympathetic nervous system, leading to blood pressure (BP) reduction. Methyldopa reduces both supine and standing BP with infrequent symptomatic postural hypotension.

Methyldopa reduces vascular resistance, has no direct effect on

**Figure 1.** Mechanism of action of methyldopa



cardiac function and does not usually reduce glomerular filtration rate, renal blood flow or filtration fraction. Plasma concentrations of norepinephrine fall in association with the reduction in arterial pressure and this reflects the decrease in sympathetic tone. Although renin secretion is decreased, this is not the prime mechanism of action of methyldopa.

When administered orally, methyldopa is absorbed by an active amino acid transport. After a single therapeutic dose, the hypotensive effect occurs in two or more hours; its maximal effect is in six to eight hours, and continues with diminishing intensity for 18–24 hours. The maximum hypotensive effect after repeated doses may not occur though until the second day. On discontinuation, the BP returns to pretreatment levels in 24–48 hours. Methyldopa and its metabolites are

excreted by the kidneys with a half-life for the drug of two hours.

Methyldopa crosses the placenta and the blood brain barrier with active transfer. Methyldopa is also eliminated into breast milk, although the concentrations are thought to be too small to be harmful to the baby.

Although its side effect profile is extensive, severe adverse effects due to methyldopa have been infrequent and the side effects are minimised if the daily dose is kept below 1g. Drowsiness is one of the common side effects but it is usually transient; headache or weakness may be noted as early and transient symptoms as well. It can cause positive Coombs test in up to 20% of patients. It can potentially cause hepatotoxicity and it should be avoided in history of active hepatic disease or discontinued if there is persistent elevation of transaminases. Methyldopa can

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aggravate pre-existing – or cause – depression. Less frequent adverse reactions include orthostatic hypertension, congestive heart failure, bradycardia, vomiting, colitis, pancreatitis, diarrhoea, constipation, mouth dryness, bone marrow depression, haemolytic anaemia, Parkinsonism and nasal congestion.

### Use of methyldopa out of pregnancy

A recent Cochrane review has summarised randomised control trial (RCT) evidence in the use of methyldopa outwith pregnancy.<sup>1</sup> In a meta-analysis of trials predominantly published in the 1970s and early 1980s, the authors concluded that methyldopa (500–2250mg daily) lowers systolic and diastolic BP by a mean of 13mmHg (95% CI 6–20)/8mmHg (95% CI 4–13). They also noted that no RCT evidence was available assessing the clinical impact of methyldopa therapy on end points such as mortality, stroke, cardiovascular disease or heart failure – reflecting the reduction in clinical use of the drug in the developed world prior to the advent of large end point trials in hypertension. There are no RCTs for the use of methyldopa in patients with diabetes.

### Use of methyldopa in pregnancy

Methyldopa crosses the placenta and achieves fetal concentrations similar to maternal serum levels. Despite this, there is no obvious association with congenital abnormalities but mild hypotension has been reported in neonates in the first two days of life. The long-term safety of methyldopa in pregnancy was reported by Cockburn *et al.* in *The Lancet* in 1982.<sup>2</sup>

Hypertension in pregnancy can be classified as: (a) chronic, (b) gestational, (c) pre-eclampsia, and (d) chronic hypertension with superimposed pre-eclampsia. Hypertension has been further categorised into mild, moderate and severe.

There are limited good quality data to evaluate the effectiveness of methyldopa, or any other antihypertensive, on the treatment of chronic hypertension in pregnancy. An RCT

conducted in the USA showed that women receiving methyldopa were as likely as women in the no-treatment group to develop pre-eclampsia (OR=1.21; 95% CI 0.55–2.65) but there was a decreased risk of developing severe hypertension.<sup>3</sup>

In the management of gestational hypertension, one trial compared methyldopa with labetalol and found that fewer women who received labetalol developed proteinuria (RR=0.04; 95% CI 0.003–0.73). Compared to placebo, methyldopa has been shown to prolong the duration of pregnancy by eight days and decrease the incidence of severe hypertension. When nifedipine was compared with methyldopa in gestational hypertension, Apgar scores were better for infants of women receiving methyldopa. More women required treatment for acute hypertension in the nifedipine group (RR=1.67; 95% CI 1.16–2.40).<sup>3</sup>

Only one RCT has compared methyldopa to placebo in women with pre-eclampsia. Women receiving methyldopa were significantly less likely to develop severe pre-eclampsia compared to women on bed rest without treatment (RR=0.18; 95% CI 0.06–0.55).<sup>3</sup>

The management of severe hypertension (systolic BP >160mmHg and diastolic BP >110mmHg) has been evaluated by several trials and summarised in a Cochrane review. There were no significant differences in outcomes but few useful comparisons as to the choice of antihypertensive.<sup>4</sup> The Royal College of Obstetricians and Gynaecologists' preferred therapeutic agents for severe hypertension in pregnancy are labetalol, nifedipine or hydralazine (Green-top guideline number 10a). The recent draft NICE guideline (full guideline April 2010) on the management of hypertension during pregnancy suggests that labetalol should be considered the first line agent for treatment of both severe and moderate hypertension in pregnancy.<sup>3</sup>

The Confidential Enquiries into maternal deaths showed that 10% of deaths due to a hypertensive disorder in the pregnancy occurred in the post-partum period, hence the importance of good control. However,

### Key points

- Methyldopa is effective in lowering blood pressure but, due to its side effect profile, has limited use out of pregnancy
- In pregnancy, including in patients with diabetes, methyldopa may be used, but labetalol is now recommended as first line for use in moderate hypertension, and labetalol, nifedipine or hydralazine as first line in severe hypertension

methyldopa is not the ideal drug for post-natal treatment due to its extensive side effect profile, in particular the risk of causing or exacerbating depression.

Methyldopa has been used successfully in pregnancies complicated with diabetes, but the data are limited and based mainly on small observational studies.

Methyldopa has no clinically significant effect on glucose tolerance and therefore no anticipated adverse interaction with diabetes.

### Conclusion

Methyldopa has for many years been the first line therapy for hypertension in pregnancy; labetalol has now taken that role but methyldopa remains a safe alternative to consider in pregnant women with chronic hypertension, gestational hypertension or pre-eclampsia. Other agents are preferred for use in severe hypertension (with or without pre-eclampsia), post-natal hypertension and out of pregnancy.

### Conflict of interest statement

There are no conflicts of interest.

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