

Labetalol

D Kernaghan, G McKay*

Introduction

Labetalol is a β blocker indicated for use in hypertension since the 1970s, including hypertension in pregnancy, hypertension with angina and hypertension following acute myocardial infarction. Given intravenously it has a role in the management of hypertensive crisis and controlled hypotension in anaesthesia. Clinically, it is most commonly prescribed as a first line agent to treat hypertensive disorders of pregnancy including pre-eclampsia.

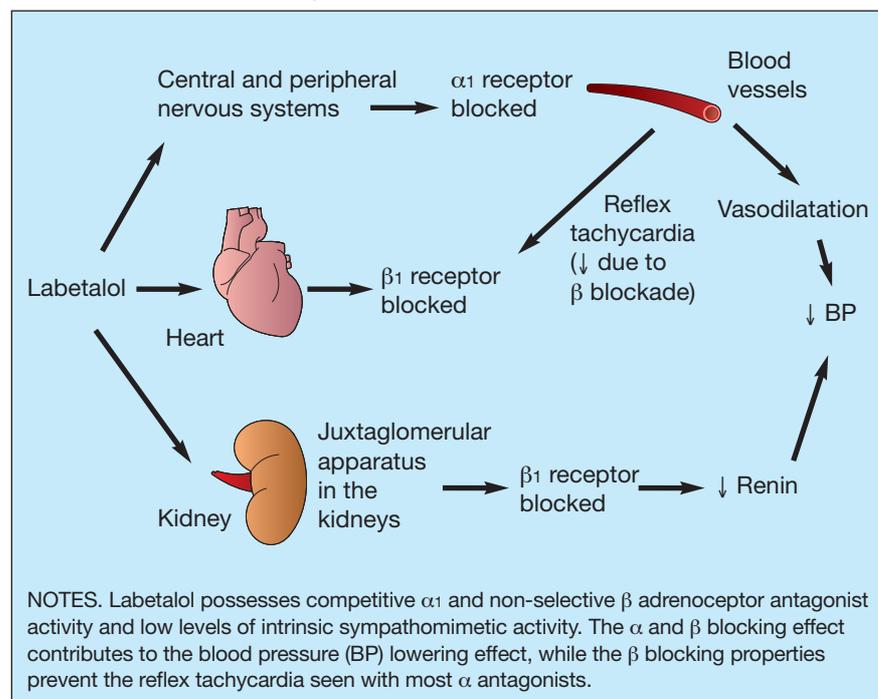
Pharmacology

Figure 1 outlines the pharmacological action of labetalol. It possesses competitive α_1 and non-selective β adrenoceptor antagonist activity and low levels of intrinsic sympathomimetic activity. The α and β blocking effect contributes to the blood pressure (BP) lowering effect while the β blocking properties prevent the reflex tachycardia seen with most α antagonists. At low doses its effect on β receptors predominates, being about a fifth of that of the β blocking effect of propranolol. At intravenous doses of 50–100mg or oral doses of 200–800mg a BP drop of approximately 20% is observed.

Labetalol has a half-life of six to eight hours and this is not altered in patients with impaired hepatic or renal function. The relative bioavailability is 100% with both oral and intravenous preparations.

Administered acutely, labetalol reduces BP rapidly with an associated decrease in total peripheral vascular resistance and a moderate reduction in heart rate and resting cardiac output. Chronic administration has been demonstrated to result in considerable reduction in BP, total peripheral resistance and a less-marked drop in heart rate and cardiac output, although with

Figure 1. The pharmacological action of labetalol



longer-term use (more than five years) this effect is lost.

Labetalol, along with carvedilol and nebivolol, is one of three β blockers, which reduce peripheral vascular resistance through vasodilatation. Labetalol has a rapid onset of action making it suitable for use in hypertensive emergencies. However, pre-clinical studies suggest that labetalol treatment does not produce nitric oxide (NO) mediated vasodilatation. Carvedilol and nebivolol do have an effect through NO mediated vasodilatation in addition to anti-inflammatory properties resulting in beneficial effects on endothelial function, not seen for labetalol.

Potential side effects of labetalol include dizziness, fatigue and nausea which are all dose related. Due to β blockade, labetalol is contraindicated

in patients with asthma due to the risk of bronchospasm. Labetalol should be used with caution in patients with type 1 diabetes with reduced hypoglycaemia awareness because of concerns that the adrenergic stress response to hypoglycaemia will be blocked by the drug.

Labetalol use in hypertension

Although indicated for use in hypertension, the main use of labetalol with pregnancy is in the management of hypertensive emergencies. The combination of its rapid onset of action and vasodilator properties ensures a prominent role in the management of accelerated hypertension. Although both the oral and intravenous routes have fast onset of action, the intravenous formulation allows for use in encephalopathic patients or

Dawn Kernaghan, MD, MRCOG,
Specialist Registrar in Obstetrics and
Gynaecology, Princess Royal Maternity
Hospital, Glasgow, UK
Gerry McKay, BSc(Hons), FRCP,

Consultant Physician, Glasgow Royal
Infirmary, Glasgow, UK

*Correspondence to: Dr Gerry McKay,
Consultant Physician, Wards 3, 4 & 5,

Glasgow Royal Infirmary, 84 Castle Street,
Glasgow, UK; email:
gerard.mckay@ggc.scot.nhs.uk



Labetalol

in patients presenting with seizures where the oral route is compromised. With a wide dosing range it can be titrated against BP, limiting large fluctuations in BP and avoiding significant cerebral or renal hypoperfusion.

Labetalol should also be considered for use in women with essential hypertension who are planning pregnancy. It should therefore be one of the therapeutic options available when counselling women preconception with hypertension, particularly given that some of the alternative newer antihypertensives such as ACE inhibitors are known teratogens.

Use of labetalol in pregnancy

Labetalol is the drug of choice for treatment of gestational hypertension and pre-eclampsia. The most recent Confidential Enquiry into Maternal Deaths, 'Saving Mother's Lives', reported on the deaths of 18 women from eclampsia or pre-eclampsia. Intracranial haemorrhage was the single most common cause of death with lack of effective antihypertensive treatment cited as the most common cause of sub-standard care.¹ Although antihypertensive therapy does not alter the development of complications of disease progression in pre-eclampsia such as seizures, renal failure and coagulopathy, it reduces the risk of maternal intracranial haemorrhage. Recent NICE guidance on the management of hypertensive disorders during pregnancy recommends oral labetalol as first line treatment to keep diastolic BP between 80–100mmHg and systolic BP <150mmHg in the management of gestational hypertension and pre-eclampsia.²

Short-term outcomes of beta blockers in pregnancy

A Cochrane review of oral β blockers for mild to moderate hypertension in pregnancy was published in 2009. Compared to no therapy or placebo, β blockers are associated with an increase in small for gestational age infants. In this review, the trial which demonstrated the strongest association between β blockers and small for gestational age infants was a small study of 15 patients who took atenolol from the first trimester of pregnancy onwards. Limitations of this individual study, apart from the small numbers,

are that intrauterine growth restriction may be especially associated with atenolol rather than a class effect associated with all β blockers, and that the drug was started in the first trimester.³ This Cochrane review also found that β blockers appear to be associated with an increase in neonatal bradycardia and a reduction in respiratory distress syndrome. Few studies within the review reported on these outcomes, but, of the infants who developed bradycardia, none required treatment, suggesting that it is not clinically significant.

Long-term outcomes of labetalol in pregnancy

Although labetalol has been in use for over three decades, there is a paucity of data on long-term outcomes in children born to mothers taking it in pregnancy. A Dutch historical cohort study examined the functional development of 202 children born after treatment of mild-to-moderate gestational hypertension with labetalol versus methyl-dopa and no antihypertensive treatment. Labetalol exposure in-utero appeared to increase the risk of attention deficit hyperactivity disorder (ADHD) (OR 2.3; 95% CI 0.7–7.3), while methyl-dopa exposure might influence sleep (OR 3.2; 95% CI 0.6–16.7). However, the findings were not statistically significant and, in addition, the study had major methodological flaws impacting on the clinical interpretation such as failing to control for gestational age.⁴

In a smaller prospective cohort study of 32 mother–child pairs with matched controls where labetalol had been taken antenatally, no adverse effect on neurocognitive development was seen.⁵

Both of these studies only assessed women who had gestational hypertension or pre-eclampsia. There remains no randomised controlled trial or well-conducted cohort study on the use of labetalol from the first trimester onwards.

Conclusion

Labetalol is the first line treatment for gestational hypertension and pre-eclampsia. In women with chronic hypertension, predating pregnancy, who require antihypertensive treatment in the first

Key points

- Labetalol is the preferred first line antihypertensive used in the management of hypertensive disorders of pregnancy
- Labetalol should be used with caution in the first trimester but has an overall good safety record in pregnancy
- Labetalol can be used in patients with diabetes who require antihypertensive treatment in pregnancy, but with caution in those with reduced hypoglycaemia awareness

trimester of pregnancy, the potential benefits of treatment should outweigh risks, but informed consent should be obtained from the woman. There is an increasing prevalence of diabetes in pregnancy including women with type 1 diabetes, type 2 diabetes and gestational diabetes. Some of these individuals will need antihypertensive treatment before and/or during pregnancy. Diabetes should not be considered a contraindication for using labetalol; however, in addition to being alert to potential problems with intrauterine growth, where relevant the individual pregnant woman should be assessed for risk of hypoglycaemia, and antihypertensive treatment choice made on a balance of risk and benefit to the woman and the fetus.

Declaration of interest

There are no conflicts of interest.

References

1. Confidential Enquiry into Maternal and Child Health. Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer, 2003–2005. The Seventh Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom; 2007.
2. Hypertension in pregnancy: the management of hypertensive disorders during pregnancy. National Institute for Health and Clinical Excellence, 2010.
3. Magee LA, *et al.* Expectant management of severe preeclampsia remote from term: a structured systematic review. *Hypertens Pregnancy* 2009;28:312–47.
4. Pasker-de Jong PC, *et al.* Antihypertensive treatment during pregnancy and functional development at primary school age in a historical cohort study. *BJOG* 2010;117:1080–6.
5. Chan WS, *et al.* Neurocognitive development of children following in-utero exposure to labetalol for maternal hypertension: a cohort study using a prospectively collected database. *Hypertens Pregnancy* 2010;29:271–83.