Nifedipine in pregnancy

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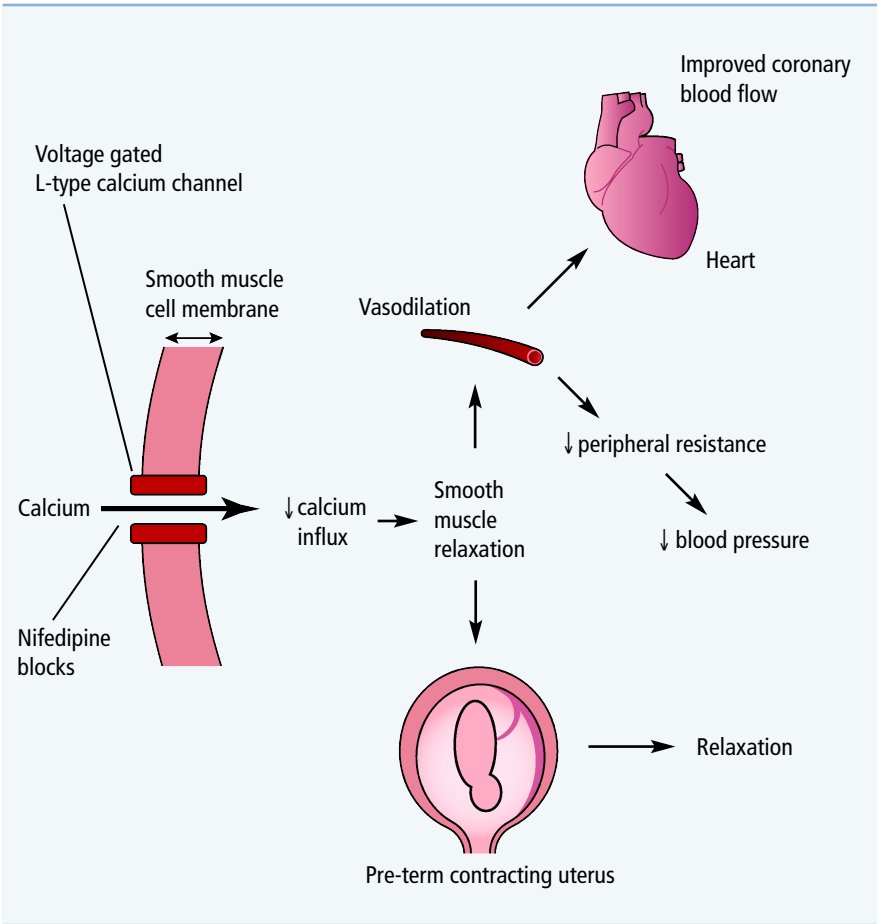

Figure 1. Nifedipine binds and blocks L-type calcium channels in smooth muscle predominantly in the coronary and peripheral vasculature, resulting in vasodilation. The effect on smooth muscle is utilised in its off-licence use as a tocolytic

Introduction

Nifedipine was the first of the dihydropyridine family of calcium channel blockers licensed for use. Studies from when it was originally developed by Bayer in the early 1970s showed that the short-acting formulation of nifedipine was effective in controlling blood pressure, but because of a rapid reduction in blood pressure had a severe side-effect profile. Because of this, newer long-acting, modified-release formulations were developed with fewer side effects. Nifedipine in its various formulations is a cheap and effective drug for oral intake. It is recommended for the control of moderate to severe hypertension, and is especially useful for treating hypertensive disorders in pregnancy the incidence of which is more common in women with diabetes. It is also licensed for treating angina.

Pharmacology

Figure 1 outlines the pharmacological action of nifedipine. Nifedipine binds to and blocks voltage-gated L-type calcium channels present in smooth muscle. This reduces calcium influx and intracellular calcium, and results in relaxation. It predominantly works in the coronary and peripheral vasculature where it results in vasodilation. Coronary vasodilation will provide a beneficial effect in angina and peripheral vasodilation a reduction in blood pressure.

Side effects of nifedipine include headache, flushing and reflex tachycardia which are less

of a problem with modified-release preparations. Another common side effect for all calcium antagonists is ankle swelling which can be minimised by using the lowest dose possible.

Nifedipine causes non-specific smooth muscle relaxation and can exert a tocolytic effect (inhibition of uterine contractions) by preventing the influx of extracellular calcium into myometrial cells. This 'off-label' use to prevent pre-term labour has been used widely with good effect.

Trials of safety and efficacy

The use of nifedipine is well established for controlling hypertension and treating angina. Previously, concerns were raised about dosage and long-term use. A sequence of meta-analyses in the 1990s raised questions about the safety of nifedipine culminating in a meta-analysis in 1999 which reports an adverse effect on cardiovascular events in patients with stable angina due to an increased frequency of angina. However, this effect was only seen for patients treated with immediate-release nifedipine monotherapy, and was likely to be due to an abrupt vasodilation with a reflex sympathetic activation.

Since then, two large randomised controlled trials with a long-acting formulation of nifedipine have demonstrated a reduction in angina with no increase in major adverse coronary events when compared to placebo in patients with stable angina, and comparable efficacy and safety when compared to a diuretic in patients with hypertension. Both trials included a substantial number of patients with diabetes.

Nifedipine use in pregnancy

Nifedipine is an appropriate second-line antihypertensive drug during pregnancy. The short-acting, sublingual form has been withdrawn from use on the manufacturers' advice due to adverse effects on the cardiovascular system as described above. Modified-release preparations have a better side-effect profile, with a good therapeutic effect in lowering pregnancy induced hypertension. The common side effects include flushing, headache and chest pain. No trials have been identified for effectiveness of nifedipine in chronic hypertension during pregnancy.

A randomised controlled study on 126 women in Sri Lanka compared the effectiveness of nifedipine and methyldopa in treating pregnancy induced hypertension. No statistically significant differences were found for the incidence of placental abruption, HELLP syndrome (Haemolysis, Elevated Liver enzymes, Low Platelet count), eclampsia, caesarean section, maternal side effects, birth weight, intrauterine death or maturity at delivery.[1] A review of the use of nifedipine in pregnancy concluded that nifedipine provides maternal benefit by lowering blood pressure, reducing the risk of cerebral haemorrhage and end-organ damage. Perinatal effects of nifedipine are yet to be established.[2]

Short-term outcomes of nifedipine use in pregnancy

In a prospective cohort study of 78 women who took nifedipine from the first trimester onwards, there was no increased risk of teratogenicity.[3] A randomised controlled trial allocated women who developed pre-eclampsia remote from term to treatment with nifedipine and bed rest versus bed rest alone. While nifedipine reduced blood pressure, there was no effect on hospitalisation or perinatal outcome.[4]

Long-term outcomes of nifedipine use in pregnancy

There are no long-term data for children born to mothers treated with nifedipine for hypertension. There are two studies that evaluated several long-term outcomes in children born to mothers who were treated with nifedipine for tocolysis during pregnancy.[5,6] A Dutch study looked at the long-term psychosocial and motor effects on children exposed *in utero* to nifedipine or ritodrine for the management of pre-term labour. No long-term differences were identified between the two groups. Similarly, no difference was noticed in the developmental scores at two years of age in children born to mothers who were randomised to nifedipine versus those who received ritodrine.

Key points

- Nifedipine is a cheap, effective and safe antihypertensive drug, which is most effective in treating moderate to severe hypertension
- It is a second-line antihypertensive drug used to treat pregnancy-related hypertension, which is more common in women with diabetes, and may also be used to prevent pre-term labour
- Modified-release preparations are favoured because immediate-release preparations are associated with unwanted side effects

Discussion

Modified-release preparations of nifedipine are useful agents for the management of angina and hypertension. They are also a safe and effective option for gestational hypertension and pre-eclampsia. They may be useful to control blood pressure in women with chronic hypertension planning pregnancy. There is an increased prevalence of hypertension in pregnant women with diabetes. Some of these individuals will need blood pressure treatment, and long-acting, modified-release preparations of nifedipine are part of the therapeutic armoury that is known to be safe and effective in this setting.

Declaration of interests

There are no conflicts of interest declared.

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