Nifedipine trials: effectiveness and safety aspects

Herman P. van Geijn, Joris E. Lenglet, Annemieke C. Bolte

Nifedipine (Adalat) is marketed as an anti-hypertensive agent. Nifedipine inhibits voltage-dependent L-type calcium channels, which leads to vascular (and other) smooth muscle relaxation and negative inotropic and chronotropic effects on the heart. Vasodilation, followed by a baroreceptor-mediated increase in sympathetic tone then results in indirect cardiostimulation. Nifedipine was introduced as a tocolytic agent at a time when β-agonists and magnesium sulphate dominated the arena for the prevention of preterm birth. The oral administration route, the availability of immediate and slow-release preparations, the low incidence of (mild) side effects, and its limited costs explain the attraction to this medication from the obstetric field and its rapid and widespread distribution. Currently, over 40 studies have been published on nifedipine’s tocolytic effectiveness, including seven meta-analyses. The quality of the studies suffers particularly from performance bias because the majority of them failed to ensure adequate blinding to treatment both for providers and patients. Concerns about other methodological flaws include measurements, outcome assessment and attrition bias. In particular, the safety aspects of nifedipine for tocolysis have been underassessed. Conclusions from the meta-analyses, favouring the use of nifedipine as a tocolytic agent, are not supported by close examination of the data. The tocolytic effectiveness and ‘safety’ of nifedipine has been studied primarily in normal pregnancies. Based on its pharmacological properties, one should be cautious to administer nifedipine when the maternal cardiovascular condition is compromised, such as with intrauterine infection, twin pregnancy, maternal hypertension, cardiac disease, etc. Life-threatening pulmonary oedema and/or cardiac failure are definite risks and have been reported. Under such circumstances, the baroreceptor-mediated increase in sympathetic tone may not balance the cardiac-depressant activity of nifedipine.

INTRODUCTION

Spontaneous preterm birth is the leading cause of infant morbidity and mortality. Spontaneous preterm labour and preterm birth can be attributed to the following:

1. abnormal stretching of the uterus due to multiple pregnancy and polyhydramnios;
2. abnormal stimulation of the uterus due to intrauterine bleeding, intrauterine infection, maternal hyperactivity or stress; and
3. insufficient support at the cervical internal os due to repeated late abortions, conisation of the cervix or diethylstilbestrol (DES) exposure.

Often combinations of these conditions exist (e.g. a twin pregnancy in a congenitally malformed uterus when abnormal stretching and stimulation as well as insufficient support are involved). A cascade of increased pressure on the uterine wall and cervix, loss of cervical mucus, entry of bacteria, chorioamnionitis and increased uterine contractility may be the result.

Whatever the cause of threatened preterm labour, it may be necessary to administer tocolytics, particularly at the very early gestational ages (i.e. 24–30 weeks of pregnancy). A great variety of tocolytics have entered obstetric practice in the last two decades: alcohol, magnesium sulphate, β-agonists, prostaglandin synthesis inhibitors, progestins, cyclooxygenase inhibitors, calcium channel blockers, nitric oxide donors and more recently oxytocin receptor antagonists.1,2 Currently, only two products have been registered for tocolysis for a maximum duration of 48 hours: the β-agonist, ritodrine (Prepar), and the oxytocin antagonist, atosiban (Tractocile).

Other approaches to reduce the risk of preterm delivery have involved nutritional adjustments, reduction of workload, less physical activity and stress and some form of bed rest. Nutritional adjustments that have been advocated are folic acid, calcium, zinc, magnesium, selenium and iron supplementation, intake of fish oils and increased consumption of fish.3

TOCOLYSIS AT THE END OF 1980s AND EARLY 1990s

At the end of the 1980s, and during the early 1990s, the focus was on β-agonists for the treatment of preterm uterine contractions. The β-agonists used included isoxuprime, hexaprenaline, terbutaline, salbutamol, fenoterol and
ritodrine.1 The administration used was both intravenously and orally, the latter preferably in the form of slow-release preparations. Gradually, it became evident that the efficacy of β-agonists was doubtful for the prevention preterm birth. Prolongation of pregnancy was only effective for a maximum of 48 hours due to the development of tachyphylaxis and their use was not associated with an improvement in perinatal outcome.4

Many serious side effects have been reported with β-agonists, such as hypotension, tachycardia, headache, tremor, nausea, anxiety and disturbances in metabolism (i.e. elevated liver enzymes, hypokalaemia and hyperglycaemia).1–5

Maternal pulmonary oedema has also been reported, particularly when β-agonists are combined with corticosteroids to promote lung maturity of the fetus and excessive intravenous maternal fluid load. The application of β-agonists under these circumstances can be a substantial risk to the life of the mother. Treatment with the powerful β-agonists can result in maternal death.6,7

Finally, the β-agonists cause an increase in fetal heart rate, frequently up to the level of baseline tachycardia, which complicates the interpretation of the cardiotocogram and correct assessment of the condition of the fetus.

THE INTEREST IN NIFEDIPINE FOR TOCOLYSIS

Nifedipine is one of the many calcium channel blockers, which act by blocking the influx of calcium through voltage-dependent calcium channels. Nifedipine acts on the L-type calcium channels involved with calcium influx into the cell. This results in relaxation of the smooth muscle cells. The ability of nifedipine to vasodilate the systemic and pulmonary vasculature, the reversibility on stopping the drug and its lack of tachyphylaxis has made it very popular for the treatment of acute and chronic hypertension and angina pectoris.8 In pre-eclampsia, nifedipine effectively lowers blood pressure.9

The relaxation of the uterine smooth musculature has also been demonstrated in vitro in pregnant and non-pregnant tissue specimens.10 Nifedipine reduces the basal tone and the amplitude and frequency of spontaneous- and oxytocin- or prostaglandin-induced contractions.11,12 Nifedipine easily crosses the placenta with a ratio of 0.93 between umbilical cord blood and maternal serum concentrations.13,14

Several reviews have been published on the pharmacology and actions of calcium channel blockers used during pregnancy, in particular on nifedipine.9,10 The lower incidence of side effects in comparison with β-agonists undoubtedly has been the prime incentive to start the use of calcium channel blockers for tocolysis.15–18 The side effects also appear to have less impact on maternal wellbeing and are of shorter duration.5,19

The direct maternal adverse effects are related to the vasodilation caused by nifedipine and are primarily headache and facial flushes. Generally, these complaints disappear within 24 hours. Other potential side effects include hypotension, reflex tachycardia, dizziness, nausea and increased levels of the liver transaminases.20

Other factors that have contributed to the growing interest in nifedipine as a tocolytic are the availability of a wide range of immediately acting and extended-release preparations for oral use and the fact that it is very cheap. The dislike of both IV magnesium sulphate and the β-agonists by obstetricians during the 1990s explains the rapid widespread use of the calcium channel blockers, including nifedipine, in spite of the knowledge that none of them had ever been registered for use during pregnancy or have been compared in placebo-controlled trials.

STUDIES ON NIFEDIPINE FOR TOCOLYSIS

Currently, seven meta-analyses have been published on the use of nifedipine for tocolysis.21–27 Nifedipine has been compared with no treatment, any other tocolytic agent or any β-agonist agent.21–28 Outcome criteria were based on the incidence of preterm birth at various gestational ages, prolongation of pregnancy duration, a long list of neonatal outcome parameters and the incidence of side effects.

One meta-analysis addressed the role of maintenance therapy with calcium channel blockers versus no treatment.27 Only one study could be found with nifedipine maintenance therapy and this showed no benefit.29 A similar result was recently published by Sayin et al.30 They showed a gain in gestational age at the moment of birth following maintenance therapy with nifedipine at a dose of up to 80 mg per day, after initial intravenous tocolysis with ritodrine and verapamil. Maintenance therapy did not decrease the recurrence of preterm labour episodes or improve perinatal outcome.30

The meta-analysis by Coomarasamy proposes an indirect comparison of nifedipine versus atosiban for tocolysis in preterm labour.4,6 Both compounds have never been compared in a randomised fashion, the most likely reason being that nifedipine has not been registered for use in pregnancy and never will be (Bayer, personal communication).

The most homogeneous comparison, comprising a sufficiently large number of women, concerns the comparison of any calcium channel blocker with any β-agonist agent.15,16,19,31–36 A summary of the most relevant data is provided in Table 1. The comparison is on the outcome parameters: delay of delivery for more than 48 hours and seven days, the incidence of respiratory distress syndrome (RDS) and the incidence of treatment withdrawal. All are in favour of the calcium channel blockers, of which nifedipine was the most frequently used. The weight of the studies of Papatsonis et al.37,38 in these meta-analyses is between 37% and 62%. The Papatsonis trials differed from other randomised controlled trials on two important issues: high doses of nifedipine were used, often up to 160 mg nifedipine retard, and maintenance therapy was used.
Table 1. Meta-analysis of calcium channel blockers versus β-agonists.23,24

<table>
<thead>
<tr>
<th></th>
<th>No. of studies</th>
<th>No. of patients</th>
<th>Odds ratio</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>Birth &lt;48 hours</td>
<td>6</td>
<td>470</td>
<td>0.72</td>
<td>0.53–0.97</td>
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<tr>
<td>Birth &lt;7 days</td>
<td>2</td>
<td>242</td>
<td>0.76</td>
<td>0.59–0.99</td>
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<tr>
<td>RDS</td>
<td>7</td>
<td>552</td>
<td>0.64</td>
<td>0.45–0.91</td>
</tr>
<tr>
<td>Treatment withdrawal</td>
<td>7</td>
<td>542</td>
<td>0.09</td>
<td>0.02–0.38</td>
</tr>
</tbody>
</table>

Adequacy of the nifedipine studies according to current standards

Most of the studies comparing nifedipine for tocolysis with no treatment or any other agent suffer from a limited number of women recruited. In the largest study by Papatsonis et al.,37,38 95 women on nifedipine were compared with 90 women on ritodrine treatment. Randomisation was performed with sealed envelopes. It was a multicentred study performed between February 1, 1992, and February 1, 1995, but received no external financial support. The doses of the extended-release nifedipine varied from 60 to 160 mg.

The different types of formulation and doses of nifedipine applied in the numerous trials varied considerably, for example, the use of immediately acting versus extended-release nifedipine. Adequate selection, power analysis, concealment of allocation, stratified randomisation, blinding to treatment, blinding to outcome and intention-to-treat analysis were very frequently not performed, resulting in substantial performance, measurement and attrition biases.39 The best results that can be calculated from a clinical study require correct patient selection and using an intention-to-treat analysis. These criteria were only fulfilled in 23% and 29% of the randomised controlled trials, respectively.40 Study quality is the Achilles heel of primary research on the use of nifedipine for tocolysis as well as those meta-analyses based on these studies.39,40

Safety of nifedipine for tocolysis

There are various forms of nifedipine: immediate-release capsules of 10 mg and extended-release tablets of 20 (Adalat retard), 30 (Adalat oros), 60 and 90 mg. The usual maintenance dose is 30–60 mg once daily for the treatment of hypertension in the non-pregnant situation. Titrating to doses above 90 mg daily is not recommended. In this report, most of the randomised controlled trials on nifedipine for tocolysis have started with immediate-release tablets or capsules up to a maximum dose of 40 mg during the first hour. The extended-release medication varied from 60 to 160 mg daily.21–38 From these studies, a great variety of side effects have been reported with nifedipine. As there are no well-controlled studies in pregnant women, the recommendation of the Bayer Company is to avoid nifedipine during pregnancy.41 It is a category C drug, which means that it can only be used if the potential benefit justifies the potential risk to the fetus. There is no recommendation when to avoid it for specific maternal reasons. General warnings concern the risk of excessive hypotension, myocardial infarction and congestive heart failure.41 All of these serious adverse events are not readily distinguishable from the natural history of preterm labour.

From the literature, myocardial infarction has been reported in about 4% of women and congestive heart failure or pulmonary oedema in about 2% of women on extended-release nifedipine. It remains possible that some or many of these events are drug related. As a result, in a number of countries, the immediate-release tablets have been taken off the market because of their rapid onset, which may provoke myocardial infarction in already cardiovascular-compromised patients.42 Contrary to ritodrine, nifedipine had minimal effects on maternal pulse rate, systolic and diastolic blood pressure, serum potassium concentrations and blood glucose levels.5

Nifedipine is used both for tocolysis and the treatment of pre-eclampsia. In pre-eclampsia, nifedipine lowers systolic and diastolic blood pressure without apparently decreasing uteroplacental blood flow.43–46 Although concerns about the effect on the fetus may be balanced by the information from Doppler studies, concerns on possible effects of nifedipine on the maternal cardiovascular circulation remain. Only limited information is available; the most detailed information is from Papatsonis et al.5

It is, however, to be noted that Papatsontis excluded multiple pregnancy, documented intrauterine infection, a
clinical diagnosis of placental abruption, diabetes mellitus, cardiovascular disease, hyperthyroidism and severe pre-eclampsia in his study. Some of the exclusions were because of potential negative effects on the maternal condition from the use of ritodrine in the other study arm.

Table 2 presents seven recent cases collected within the Vrije Universiteit Medical Center (VUmc) of severe maternal dyspnoea (with artificial ventilation in four out of the seven cases), where nifedipine tocolysis was suspected as the cause or at least could not be excluded. In all cases nifedipine was stopped, which was then followed by rapid maternal recovery. Six out of the seven cases concerned a twin pregnancy, and in four out of the seven cases there was evidence for (subclinical) chorioamnionitis.

Further recent case reports (Table 3) also lead us to the conclusion that the use of nifedipine or any other calcium channel blocking agent for tocolysis is potentially dangerous to the mother, certainly if the maternal cardiovascular condition is or may be compromised.47–50

Nifedipine exerts both vascular and cardiac effects. It vasodilates the vessels and exerts negative inotropic and chronotropic effects depressing the heart.51 The vascular/cardiac ratio for nifedipine is 10:1. The cardiodepressant effect of nifedipine is in vivo counteracted by a vasodilation-triggered and baroreceptor-mediated reflex increase in sympathetic tone resulting in indirect cardiostimulation. The increase in sympathetic tone compensates for the negative inotropic and chronotropic action by nifedipine on the heart.51 It is imaginable that under certain circumstances in which vasodilatation is enhanced as in multiple gestations, intrauterine infection, etc., the sympathetic-induced compensation on the heart remains absent with the use of nifedipine. The vessels may have dilated to such an extent that the baroreceptor response is not elicited and the increase in sympathetic tone does not occur. The end result will be that the cardiodepressant action of nifedipine prevails, leading to dyspnoea and hypoxia or enhanced pulmonary oedema.

The hypotensive, negative inotrope and chronotrope actions of nifedipine may under certain circumstances also endanger the life of pregnant women suffering from a cardiac disease (whether or not known) or when the mother develops cardiomyopathy during pregnancy.

CONCLUSION

To guarantee the safety of nifedipine for use during pregnancy, future large, well-designed and well-controlled studies are required. Until then, caution is advised with the use of nifedipine for tocolysis, particularly if there are complications of pregnancy.

References


