

Side-effect and vital sign profile of nifedipine as a tocolytic for preterm labour

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Objective To examine the side-effect and vital sign profile of nifedipine used as a tocolytic.

Design Retrospective audit.

Setting Tertiary care university hospital, Hong Kong.

Patients Women presenting with preterm labour (before 34 weeks of gestation) between March 2001 and September 2004.

Main outcome measures Maternal heart rate, blood pressure, and foetal heart rate were monitored regularly. A four-point Likert scale multiple-choice questionnaire was used to assess the perceived degree of flushing, headache, nausea, dizziness, and shortness of breath. All assessments were performed at predefined intervals from the onset of treatment. Repeated measures analysis of variance was performed to identify any time-dependent association with nifedipine treatment.

Results In all, 212 episodes of preterm labour were treated with nifedipine in 203 women. In 120 episodes, preterm labour was suppressed for more than 48 hours. Treatment was discontinued in three women because of profound hypotension ($<90/60$ mm Hg), and in one because of severe flushing. Only one patient developed maternal tachycardia (≥ 140 beats per minute), and in two foetal tachycardia (≥ 180 beats per minute) was encountered. Moderate headache was experienced in nine women, flushing in nine, dizziness in four, nausea in three, and shortness of breath in one. Repeated measures analysis of variance with time of measurement revealed a significant reduction in maternal blood pressure and increase in maternal heart rate that plateaued after 1 hour of therapy. The foetal heart rate returned to baseline values 3 hours after commencing therapy.

Conclusion In general, use of nifedipine as the first-line tocolytic was safe. However, severe maternal hypotension can occur and close monitoring of vital signs is warranted.

Key words

Nifedipine; Obstetric labor; Premature;
Tocolysis

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Introduction

Nifedipine is a type II calcium channel antagonist, which inhibits the influx of calcium ions into myometrial and other cells and thereby reduces muscle contractility.¹ It reaches peak plasma levels within 45 to 60 minutes after being taken orally and has a plasma half-life of 2 to 3 hours.² It has been shown in vivo and in vitro to be an effective tocolytic agent for suppressing uterine activity. Its ability to suppress preterm labour was first reported in 1980.^{3,4}

The Royal College of Obstetricians and Gynaecologists Guideline No. 1(B) recommended that whenever required, nifedipine or atosiban (an oxytocin receptor antagonist) be used as preferred first-line tocolytic agents, in preference to beta-sympathomimetics.⁵ This was because nifedipine appeared to be a more effective agent and conferred significantly fewer maternal side-effects. Nifedipine has become more popular in the management of preterm labour due to its low cost and ease of administration. Its use is likely to increase further after the Cochrane database reviews endorsed the preferential use of calcium channel blockers over other tocolytics. These reviews also indicated that the incidences of maternal adverse drug reactions and those leading to cessation of therapy were 15.6% and 0.2% respectively, which were significantly lower than the corresponding values (48.7% and 7.0%) encountered in those receiving other tocolytics.⁶

硝苯地平應用在早產宮縮抑製中的副作用及對生命徵象的影響

目的 評估硝苯地平的副作用及對生命徵象的影響。

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患者 由2001年3月至2004年9月之間，入院及在34孕周前有早產徵象的婦女。

主要結果測量 定期量度的孕婦心跳率，血壓和胎兒心跳率。用李克強四等尺量表測量孕婦不同程度的面紅、頭痛、作嘔、頭暈和氣喘。全部的測量都是在既定的時間點上執行的。使用變異分析重複測量統計來測試開始治療後不同時間的影響。

結果 在203個孕婦中，有212人次接受硝苯地平的治療。其中的120人次，早產宮縮可以被抑製超過48小時。有3個和1個孕婦分別因發現低血壓(<90/60 mm Hg)和面紅而需要停止治療。另外，只有1個孕婦心跳過速(≥ 140 bpm)及兩個孕婦的胎兒心跳過速(≥ 180 bpm)。副作用包括頭痛(9個)、面紅(9個)、頭暈(4個)、作嘔(3個)和氣喘(1個)。重複測量變異數分析顯示在第1個小時，孕婦血壓有明顯的減少及孕婦心跳有明顯的增加。胎兒心跳在第3個小時回復到最初的狀態。

結論 總括而言，硝苯地平作為宮縮抑製藥是安全的，但低血壓仍有機會發生。所以必須要維持緊密的生命徵象監察。

It is well known that tocolytic agents used for suppression of labour can have significant adverse cardiovascular effects on both the mother and foetus. Although nifedipine was considered to be associated with a significantly lower incidence of maternal and foetal side-effects than alternatives, it has vasodilating properties which can induce tachycardia, headaches, nausea, hot flushes, palpitations, severe hypotension, and even pulmonary oedema. Moreover, a recently published review suggested that the adverse events related to nifedipine use may be more frequent than initially thought.⁷

The objective of the current study was to investigate the side-effect profile of nifedipine over the first 3.5 years of its use in our unit, as the first-line tocolytic agent to suppress preterm labour.

Methods

Study population

This was a retrospective audit in a university hospital with an annual delivery rate of about 6000. All women presenting in preterm labour from 24 to 33 weeks of gestation between March 2001 and September 2004 were included. Preterm labour was defined as regular painful uterine contractions, at a frequency of 2 or

more per 10 minutes, regardless of whether there had been cervical changes. To improve homogeneity of the study population, only women for whom tocolysis with nifedipine was not contra-indicated were included.

Exclusion criteria

Exclusion criteria for tocolytic therapy were signs of abruptio placentae, intrauterine infection, foetal distress, or cervical dilatation of more than or equal to 5 cm.

Treatment administration

Upon diagnosis of preterm labour, a course of dexamethasone (6 mg at 12-hour intervals for 4 doses) was given, unless delivery was considered imminent. All women were nursed in the lateral position. The tocolytic regimen adopted was based on a randomised multicentre trial comparing nifedipine and ritodrine in the management of preterm labour⁸ and is illustrated in Figure 1. Plain nifedipine was used sublingually in the initial 4 doses (every 15 minutes), then swallowed in the subsequent 3 days, and finally followed by oral nifedipine GITS (a sustained release formulation taken once daily) to improve compliance.⁹ If preterm labour recurred, nifedipine was re-initiated with sublingual loading doses followed by swallowed doses for 3 days and then regular nifedipine GITS dosing was resumed. Failure of nifedipine was defined as persistent uterine contractions after the initial sublingual doses or their recurrence despite use of maximum maintenance doses. If so, second-line tocolytics (beta-sympathomimetics or sulindac) were considered; the choice depended on clinical assessment by the attending obstetricians. Combination therapy was not used.

Treatment assessment

A locally produced computerised database was used to document each woman's details, treatment effects, and pregnancy outcome during the period of the audit. The following data were collected: demographic details, any risk factors for preterm labour, assessment of the preterm labour on admission, and whether tocolytic therapy was used. Women who received nifedipine had their heart rate (MHR), systolic (SBP) and diastolic (DBP) blood pressure, any adverse symptoms (flushing, headache, nausea, dizziness, and shortness of breath) monitored at 15-minute intervals for the first hour, and then at 2, 3, 4, 6, 8 and 12 hours after the initiation of treatment. Foetal heart rate (FHR) was also recorded at the same pre-defined intervals. Symptoms were documented using a multiple-choice questionnaire; each symptom was assessed using a 4-point Likert scale ranging from

0 (no symptoms) to 3 (severe symptoms). Maternal tachycardia was defined as a MHR of ≥ 140 beats per minute, hypotension as a blood pressure of $< 90/60$ mm Hg and foetal tachycardia as a FHR of ≥ 180 beats per minute.

Statistical analysis

All the data were entered prospectively in a pre-defined data information sheet. The Statistical Package for the Social Sciences (Windows version 14.0; SPSS Inc, Chicago [IL], US) was used for analysis of all data. Differences in categorical and continuous data were assessed using the Chi squared test and Student's *t* test, respectively. Maternal and foetal vital signs were analysed using repeated measures analysis of variance (ANOVA) with time of measurement as the within-subject factor to test whether any time-dependent relationship existed. A *P* value of 0.05 or lower was considered statistically significant.

Results

A total of 286 women, having 308 episodes of preterm labour, were admitted during the audit period. Seven (2.4%) of them were non-Chinese. Twenty-two (7.7%) women had repeated admissions requiring further nifedipine doses despite maintenance nifedipine therapy. Tocolytics were prescribed in 217 (70.5%) episodes. The main reasons for not prescribing any tocolytic therapy (in 69 women) included: rupture of membranes prior to labour (10.1%), cervical dilatation of more than 5 cm (7.5%), and concomitant antepartum haemorrhage (7.1%).

The median maternal age was 30 (interquartile range [IQR], 26-34) years and the median gestational age was 30.6 (IQR, 27.5-32.0) weeks. One hundred and fifty-one women (52.8%) were nulliparous, while 103 (36.0%) were of parity one. Two hundred and fifty-seven (89.9%) women had a singleton pregnancy.

Nifedipine was used as the first-line tocolytic in 212 (98%) of the episodes in 203 women. Among them, 116 (57%) were nulliparous and 184 (91%) had a singleton pregnancy. Eight (4%) of them had had a previous preterm delivery, while six (3%) had had a previous mid-trimester spontaneous miscarriage. Four (2%) had received elective cervical cerclage, because of a prior history suggesting cervical incompetence. Eight (4%) and none had gestational diabetes mellitus and cardiovascular disease respectively, during the index pregnancy. Fourteen (7%) were known to have had vaginal group B streptococcus colonisation.

Five episodes were excluded from further analysis because other tocolytics (beta-sympathomimetics in four and sulindac in one) were used as the first-line treatment. There were no significant differences in demographic characteristics between women who remained in the audit and those who were excluded.

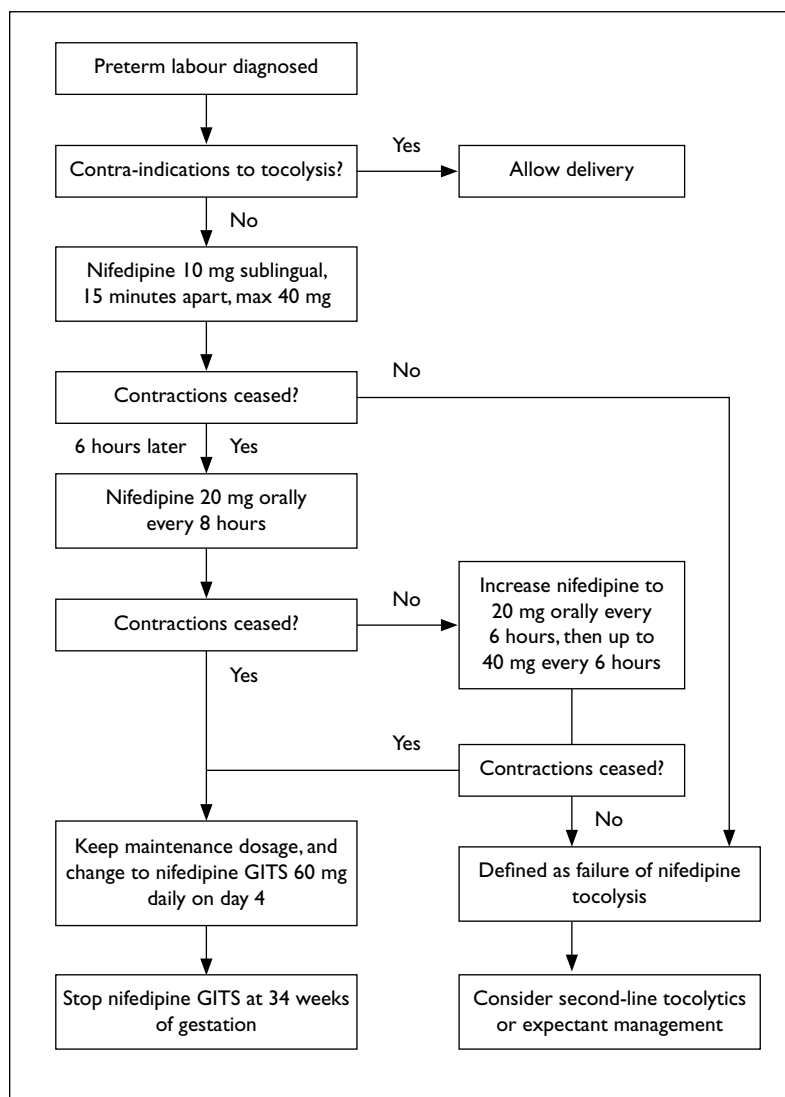


FIG 1. A flowchart showing the tocolytic regimen

Treatment efficacy

All women received the initial four sublingual doses of nifedipine. Nifedipine alone was able to suppress 120 (57%) of episodes for more than 48 hours. For the remaining patients, 49 episodes received second- or third-line tocolytics of which 21 were suppressed for more than 48 hours. Therefore, according to an intention-to-treat analysis, 141 (67%) of the episodes were suppressed for more than 48 hours by using nifedipine as initial therapy. The median number of days gained in utero was 33 (IQR, 1-62). The median birth weight and the median gestational age at delivery were 2605 g (IQR, 1675-3165 g) and 36.8 (IQR, 31.4-39.0) weeks, respectively.

Compared to successfully suppressed episodes, women with failed nifedipine treatment were more likely to have gestational diabetes mellitus (7.1% vs 1.6%), ruptured membranes (20.2% vs 8.6%), show (25.0% vs 9.4%), antepartum haemorrhage (17.9% vs

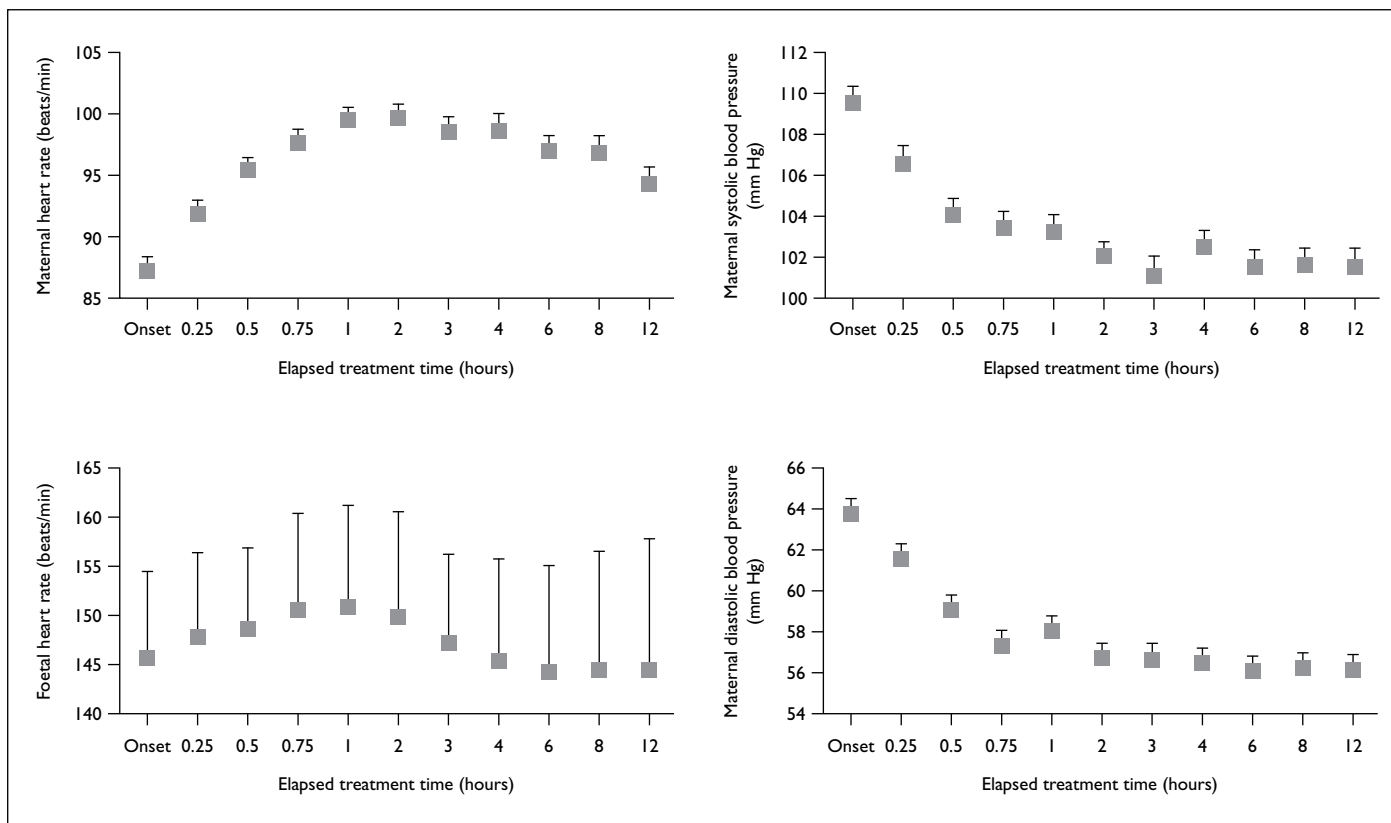


FIG 2. Means of maternal and foetal vital signs in nifedipine-treated patients during the first 12 hours, relative to values at commencement of tocolytic agent (error bars denote standard errors)

10.2%), a more dilated (median: 1 cm vs 0 cm) and shorter (median: 1 cm vs 3 cm) cervix on admission.

Maternal and foetal vital signs

The incidences of maternal tachycardia, hypotension, and foetal tachycardia were low. Maternal tachycardia was encountered in only one patient. It occurred at 30 weeks of gestation 4 hours after commencing treatment in a nulliparous woman who was in good health. Nifedipine therapy was continued and subsequent blood pressure monitoring yielded a fluctuating heart rate which remained below 140 beats per minute. This woman did not experience any other discomfort. Nifedipine needed to be discontinued in three of the episodes, due to profound maternal hypotension (<80/50 mm Hg), occurring about 2 hours after the commencement of therapy. These women were at gestational ages of 24, 30, and 32 weeks. One of them was noted before pregnancy to have occasional slow atrial fibrillation, but was in sinus rhythm throughout the preterm period and labour. Blood pressure returned to normal thereafter and there was no evidence of maternal or foetal compromise. There were two episodes of transient foetal tachycardia in two different women that occurred 60 and 90 minutes after the loading

dose. Nifedipine was not discontinued in them. All of these women had received only the 40 mg sublingual loading doses.

The exact vital sign measurements were available for 176 (83%) of the episodes. Of these, 172 (98%) and 146 (83%) had complete measurements available for the first hour and first 12 hours of treatment, respectively. Figure 2 shows the changes in estimated means for these 146 episodes, with corresponding standard errors, for maternal and foetal vital signs measured at the predefined assessment intervals.

Repeated measures ANOVA revealed that the main effect of time of measurement was significant for all four vital signs [MHR: $F(3.9,561)=21.1$, $P<0.0001$; SBP: $F(7.6,1116)=18.5$, $P<0.0001$; DBP: $F(8.02,1179)=22.5$, $P<0.0001$; FHR: $F(5.8,813)=11.8$, $P<0.0001$]. Maternal SBP and DBP both decreased linearly during the first 45 minutes of treatment [SBP: $F(2.7,462)=46.9$, $P<0.0001$; DBP: $F(8.02,1179)=22.5$, $P<0.0001$] and subsequently remained at a low level without any significant change [SBP: $F(5.2,776)=1.5$, $P=0.19$; DBP: $F(5.5,810)=1.7$, $P=0.13$] throughout the next 12 hours of monitoring. Maternal and FHR followed a similar overall trend in that both increased for the first 60 minutes of treatment [MHR: $F(3.3,565)=108.7$, $P<0.0001$; FHR: $F(3.3,531)=12.6$, $P<0.001$]. Both MHR and FHR followed downward

trends with the FHR rate returning to its baseline rate within 3 hours. Maternal heart rate remained significantly elevated after 12 hours of treatment ($P < 0.0001$).

Maternal side-effects

Overall maternal side-effects (moderate or severe) related to nifedipine were as follows: flushing in nine (4%) episodes, headache in nine (4%), nausea in three (1%), and dizziness in four (2%). Nifedipine was discontinued in only one woman because of severe flushing, which occurred within the first hour of treatment. The incidences of various symptoms within the first hour of tocolysis after consumption of the 40 mg of sublingual nifedipine were as follows: flushing in six episodes, headache in eight, nausea in three, and dizziness in one. One woman experienced a short duration of moderate shortness of breath 12 hours after therapy started, but vital signs remained stable and there was no hypoxic episode.

Discussion

After reviewing Medline (1950-2007) using the following Medical Subject Headings (MeSH): 'nifedipine', 'tocolytic agents', and 'tocolysis', it was evident that this study is currently the largest reported audit on the use of this agent as a tocolytic. Most of the previous publications were randomised controlled trials with fewer subjects, or meta-analyses of several studies rather than a single centre audit. In this audit, over half of the episodes could be suppressed for more than 48 hours, enabling completion of antenatal corticosteroid therapy. Of the episodes that were successfully suppressed for more than 48 hours, over 80% could even be prolonged for more than 7 days.

Since 2002, when the Royal College of Obstetricians and Gynaecologists advocated nifedipine and atosiban as the preferred tocolytic agents, there has been increasing debate as to which should be the first choice.¹⁰⁻¹² Despite the proven efficacy of nifedipine both from the pharmacologic aspect and clinical studies, concern over its safety has resurfaced after the publication of several reports of severe adverse reactions.⁷ In this audit, no serious maternal adverse reactions were attributed to nifedipine. Interruptions of therapy due to side-effects and concern over cardiovascular adverse reactions were uncommon (about 2%). This was higher than the 0.2% cessation rate reported in the Cochrane systematic review,⁶ and may be related to our employing greater caution in the initial years after nifedipine was used as first-line therapy, though with increasing experience this practice may have changed. In three episodes, severe maternal hypotension did occur, all at about 2 hours after starting therapy. No severe respiratory complication was encountered,

apart from one patient complaining of moderate shortness of breath (without any desaturation) for a brief period.

This audit also documented changes in MHR and blood pressure, and FHR at the commencement of tocolytic therapy. Nifedipine is a calcium channel blocker, causing peripheral vasodilatation, and as expected MHR increased in tandem with the gradual drop in blood pressure. Both parameters plateaued after about 1 hour, coinciding with the completion of the 1-hour sublingual regimen. This observation was compatible with a previous pharmacokinetic study showing a peak plasma concentration after sublingual therapy.¹³ Consistent with nifedipine crossing the placenta,¹⁴ this audit also showed the expected increase in FHR at the corresponding time. However, within 3 hours the FHR returned to baseline values, while maternal cardiovascular effects remained at plateau. This phenomenon may be related to the difference in the maternal and foetal elimination rates of nifedipine. Furthermore, over the period of the audit, no case of foetal compromise due to nifedipine therapy was encountered.

In some of the previous case reports of serious adverse reactions to calcium channel antagonists, intravenous nicardipine (a less commonly studied agent) was used instead. Intravenous administration of the latter may actually perpetuate pulmonary oedema,¹⁵ and was never used as a tocolytic agent in our hospital.

One limitation of this audit was that vital signs were documented at predefined time-points. This procedure was readily applied to maternal blood pressure and heart rate, using an automated measuring apparatus. However, for FHR which was monitored continuously, the beat-to-beat variation made it difficult to decide exactly what rate to document. This problem could have been mitigated by measuring FHR over 1 minute at the predefined time-points. Furthermore, these vital signs were monitored up to 12 hours after commencement of therapy, though subsequent changes would also have been of interest had the monitoring and documentation been extended.

Conclusion

The results of our audit indicate that in the majority of women, nifedipine is well-tolerated with regard to both vital signs and maternal symptoms. However, close monitoring is still recommended to avoid and reduce any associated morbidity when this tocolytic agent is used.

Declaration

No conflicts of interest were declared by the authors.

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