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Nifedipine for Tocolysis

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1. Two dose regimens of nifedipine for management of preterm labor: a randomized controlled trial.

Author(s): Nassar, Anwar H; Abu-Musa, Antoine A; Awwad, Johnny; Khalil, Ali; Tabbara, Jad; Usta, Ihab M

Source: American journal of perinatology; Sep 2009; vol. 26 (no. 8); p. 575-581

Publication Date: Sep 2009

Publication Type(s): Research Support, Non-u.s. Gov't Comparative Study Randomized Controlled Trial Journal Article

PubMedID: 19399705

Abstract: We compared two dose regimens of tocolytic oral nifedipine. Women with singleton pregnancies admitted in preterm labor (24 to 34 weeks) were randomized to high-dose (HD) nifedipine (N = 49; 20 mg loading dose, repeated in 30 minutes, daily 120 to 160 mg slow-release nifedipine for 48 hours followed by 80 to 120 mg daily until 36 weeks) or low-dose (LD) nifedipine (N = 53; 10 mg, up to four doses every 15 minutes, daily 60 to 80 mg slow-release nifedipine for 48 hours followed by 60 mg daily until 36 weeks). Uterine quiescence at 48 hours (primary outcome); delivery at 48 hours, 34 and 37 weeks; and recurrent preterm labor were similar. Gestational age at delivery was higher in HD (36.0 +/- 2.8 versus 34.7 +/- 3.7 weeks, P = 0.049). Rescue treatment was needed more in LD (24.5 versus 50.9%, odds ratio = 0.3; 95% confidence interval 0.1 to 0.7). Maternal adverse effects, birth weight, intensive care nursery admission, and composite neonatal morbidity were similar. However, neonatal mechanical ventilation was needed less and nursery stay was shorter in HD. HD nifedipine does not seem to have an advantage over LD in achieving uterine quiescence at 48 hours. Further studies should address the optimal dose and formulation of tocolytic nifedipine.

Database: Medline

2. Pharmacokinetics of nifedipine slow-release during sustained tocolysis.

Author(s): ter Laak, Maureen A; Roos, Carolien; Touw, Daan J; van Hattum, Paul R M; Kwee, Anneke; Lotgering, Frederik K; Mol, Ben Willem J; van Pampus, Mariëlle G; Porath, Martina M; Spaanderman, Marc E A; van der Post, Joris A M; Papatsonis, Dimitri N M; van 't Veer, Nils E

Source: International journal of clinical pharmacology and therapeutics; Jan 2015; vol. 53 (no. 1); p. 84-91

Publication Date: Jan 2015

Publication Type(s): Research Support, Non-u.s. Gov't Randomized Controlled Trial Multicenter Study Journal Article

PubMedID: 25407260

Abstract:OBJECTIVEThe pharmacokinetics of nifedipine as a tocolytic agent has not been studied in great detail in pregnant women and has instead focused on immediate release tablets and gastrointestinal therapeutic system (GITS) tablets. The aim of this study was to determine nifedipine slow-release half-life and distribution volume in pregnant women and to compare these with pharmacokinetic parameters of nifedipine in non-pregnant subjects described in the literature.MATERIALSThis is a study parallel to a trial studying women with threatened preterm labor between 26 + 0 and 32 + 2 weeks after initial tocolysis and a completed course of corticosteroids, who were randomly allocated to maintenance nifedipine (slow-release tablets 20 mg 4 times daily) or placebo. Exclusion criteria for the pharmacokinetic study were contra-indications for nifedipine, impaired liver function, and concomitant intake of inhibitors or inducers of the cytochrome P450 3A4 isoenzyme. Blood samples for measuring nifedipine plasma concentrations were drawn at t = 0, t = 12 hours, t = 24 hours, t = 48 hours, t = 72 hours, t = 7 days, and t = 9 days.METHODSPharmacokinetic parameters were estimated using iterative two-stage Bayesian population pharmacokinetic analysis by MWPharm© software. The study was designed to establish a correlation between body weight and nifedipine plasma level.RESULTSThe pharmacokinetic parameters of nifedipine slow-release tablets were determined from the data of 8 pregnant women. Nifedipine slow-release had a half-life of 2 - 5 hours, a mean distribution volume of 6.2 ± 1.9 L/kg (calculated while using a fixed biological availability of 0.45 taken from the literature due to lack of intravenous data in this population) compared to a half-life of 6 - 11 hours, and a distribution volume of 1.2 - 1.3 L/kg described in non-pregnant subjects in the literature. None of the women delivered during study medication. Study medication was continued for the duration of the pharmacokinetic study (9 days) in all women. A correlation between nifedipine plasma levels and maternal body weight was not demonstrated. This may have been caused by lack of power.CONCLUSIONPregnant subjects in this study, using nifedipine slow-release tablets, showed a larger volume of distribution and a shorter elimination half-life than for non-pregnant subjects as published in the literature.

Database: Medline

3. Nifedipine gastrointestinal therapeutic system (GITS) as an alternative to slow-release for tocolysis--tolerance and pharmacokinetic profile.

Author(s): Juon, Anna-Mengia; Kühn-Velten, W Nikolaus; Burkhardt, Tilo; Krähenmann, Franziska; Zimmermann, Roland; von Mandach, Ursula

Source: European journal of obstetrics, gynecology, and reproductive biology; Sep 2008; vol. 140 (no. 1); p. 27-32

Publication Date: Sep 2008

Publication Type(s): Randomized Controlled Trial Journal Article

PubMedID: 18394772

Abstract:OBJECTIVETo determine nifedipine plasma concentrations after a loading dose of nifedipine 10mg capsules, 40 mg over 1h followed by slow-release tablets (60 mg/d) versus gastrointestinal therapeutic system (GITS) tablets (90 mg/d) for tocolysis.STUDY DESIGNProspective study in 14 pregnant women treated for threatened preterm labor.RESULTSFollowing capsule administration there was a rapid rise in plasma concentration of drug achieving a peak of 97.5 microg/l (median) at 1h, then declined to 59.5 microg/l (median) at 5h. The concentration measured at 7200 min (120 h) was non-significantly higher in the slow-release group (median 25.5, range 6.9-67.2 microg/l) than in the GITS group (median 14.6, range 6.0-20.0 microg/l). Area under the curve (AUC) increased with the applied dose in both groups in a linear regression. Headache was more frequent in the slow-release group than in the GITS group (P=0.001).CONCLUSIONSGITS tablets 90 mg/d are an alternative dosage regimen to previous used slow-release tablets 60 mg/d for tocolysis with similar pharmacokinetic profile and a good tolerance. However, tocolysis with GITS tablets is simpler than that with slow-release tablets and may be associated with a higher compliance. GITS tablets are therefore also qualified for home monitoring.

Database: Medline

4. Nifedipine pharmacokinetics and plasma levels in the management of preterm labor.

Author(s): Papatsonis, Dimitri N M; Bos, Jacqueline M; van Geijn, Herman P; Lok, Christianne A R; Dekker, Guus A

Source: American journal of therapeutics; 2007; vol. 14 (no. 4); p. 346-350

Publication Date: 2007

Publication Type(s): Journal Article

PubMedID: 17667209

Abstract: The aim of this study was to determine if the dose regimen of nifedipine used for tocolysis was effective to achieve uterine quietness, and at which plasma concentration levels this tocolysis was achieved to optimize our dose regimen of nifedipine. In women with preterm labor, nifedipine was administered orally to achieve uterine quietness to prevent preterm birth. Patients (n = 5) were administered 10 mg nifedipine capsules (Adalat capsules, Bayer AG) orally every 15 minutes up to 40 mg in the first hour, and were subsequently given 1 tablet of 20 mg nifedipine slow release (Adalat retard, Bayer AG) t = 90 min. Plasma levels of nifedipine were measured at regular intervals during the first 4 hours after starting tocolysis. In all 5 patients tocolysis was achieved with nifedipine. Peak plasma concentration of nifedipine was 127.2 +/- 44 ng/mL at 1.2 +/- 0.1 hours. Mean plasma concentrations of nifedipine was 67.4 +/- 28.4 ng/mL. In all patients, tocolysis was achieved during the 4 hours of blood sampling. There were no adverse hemodynamic side effects seen before and after starting tocolysis with nifedipine. Initial dose regimen of 4 times 10 mg nifedipine capsule orally in the first hour, followed by 20 mg slow release nifedipine at t = 90 min is effective in achieving

tocolysis in women with preterm labor. In steady state, the mean nifedipine plasma concentration to achieve tocolysis is about the half of that measured after initial tocolysis. Use of nifedipine for preterm labor was not associated with any adverse hemodynamic side effects.

Database: Medline

5. Calcium channel blockers for the management of preterm birth: A review

Author(s): Nassar A.H.; Aoun J.; Usta I.M.

Source: American Journal of Perinatology; 2011; vol. 28 (no. 1); p. 57-65

Publication Date: 2011

Publication Type(s): Review

PubMedID: 20640972

Abstract: Preterm birth continues to be the leading cause of perinatal morbidity and mortality. A wide range of tocolytics have been utilized for the management of preterm labor. Calcium channel blockers, namely nifedipine, gained popularity as tocolytics due to the oral route of administration, availability of immediate- and slow-release preparations, the low incidence of maternal adverse effects associated with their use, and the fact that they are inexpensive. This article reviews the available literature on the clinical utility of calcium channel blockers for acute and maintenance tocolysis with special emphasis on potential adverse effects, the most appropriate dose/regimen, and contemporary practice patterns among obstetricians. There are no randomized, placebo-controlled studies demonstrating the benefit of nifedipine in preterm labor. A suggested tocolytic protocol would be to start with the lowest dose of oral immediate-release nifedipine. For the first 48 hours thereafter, all attempts should be made not to exceed 60-mg daily doses. Copyright © 2011 by Thieme Medical Publishers, Inc.

Database: EMBASE

6. Effects of fluid volume on nifedipine dissolution and absorption in humans

Author(s): Nader A.M.; Foster D.R.; Quinney S.K.; Fadda H.

Source: Clinical Pharmacology in Drug Development; Oct 2013; vol. 2 ; p. 20-21

Publication Date: Oct 2013

Publication Type(s): Conference Abstract

Available at Clinical Pharmacology in Drug Development - from Wiley Online Library

Abstract: Statement of Purpose, Innovation or Hypothesis: Immediate release (IR) nifedipine, used for preterm labor, is poorly soluble with highly variable absorption. The purpose of our studies was to evaluate effects of increasing gastric fluid volume on nifedipine dissolution and absorption in humans. Description of Methods and Materials: Nifedipine dissolution from IR capsules (10 and 20 mg "2x10") in 100, 200, and 400 ml Fasted-State-Simulated-Gastric-Fluid (FaSSGF) was determined using a USP-II standardized mini- apparatus. Using the dissolution results, a two-phase randomized crossover single dose pharmacokinetic study in six healthy volunteers was designed to determine the effect of water volume on nifedipine absorption. Subjects received a 10mg dose of nifedipine IR with 50 or 250 ml water. Blood samples were collected up to 6 hours following dosing and nifedipine plasma concentrations determined using LC/MS/MS. Nifedipine Cmax, tmax, and AUC0-6 were compared using paired t-test. Data and Results: Faster drug release and delayed precipitation were observed for 200 ml FaSSGF volume (AUCdiss=51+/-1.8 vs. 16+/-2.1 ng.hr/ml in 200 and 100ml, respectively, P<0.001). This effect was less pronounced for 20 mg doses (AUCdiss=30+/-7.5 ng.hr/ml for 400 ml vs. 17+/-2.9 ng.hr/ml for 200 ml, P=0.003). No significant differences were observed in nifedipine pharmacokinetic parameters between the two phases of the clinical study. However,

administration of 250 ml of water with nifedipine IR capsule was associated with marked reduction in Cmax variability (CV%=47% vs. 70%). In three of the subjects a 2-10 fold increase in Cmax was observed in the large volume phase. Interpretation, Conclusion or Significance: Nifedipine absorption is associated with high inter-individual variability when administered with large fluid volumes. However, the observed variability in nifedipine absorption and Cmax was reduced, warranting the use of large fluid volumes when IR nifedipine is administered for treatment of preterm labor.

Database: EMBASE

7. Nifedipine trials: effectiveness and safety aspects.

Author(s): van Geijn, Herman P; Lenglet, Joris E; Bolte, Annemieke C

Source: BJOG : an international journal of obstetrics and gynaecology; Mar 2005; vol. 112

Publication Date: Mar 2005

Publication Type(s): Journal Article Review

PubMedID: 15715601

Abstract: 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 beta-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 under-assessed. 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.

Database: Medline

8. Comparison of two nifedipine formulations for inhibition of preterm labor

Author(s): Salazar L.; De Guirior C.; Escura S.; Migliorelli F.; Palacio M.

Source: Journal of Maternal-Fetal and Neonatal Medicine; 2016; vol. 29 ; p. 298-299

Publication Date: 2016

Publication Type(s): Conference Abstract

Abstract: Introduction: The relative safety, maternal tolerance, ease of administration and reduction in adverse neonatal outcomes by significantly delaying delivery, support the use of nifedipine as a first choice for inhibition of preterm labor. Recently, the Spanish Agency of Medicines and Devices (AEMPS) approved a new oral solution of nifedipine specially designed to be used in preterm labor management. The aim of this study was to compare the use, perinatal outcomes and side-effects between these two nifedipine formulations used in the clinical practice Materials and methods: Retrospective study in a tertiary center between January 2012 and December 2015 including women admitted because of preterm labor, in which nifedipine was the first tocolytic agent used. Only singleton pregnancies were included. Maternal and perinatal outcomes were compared based on whether nifedipine capsules or nifedipine oral solution were used for tocolysis. A descriptive study was carried out on qualitative and quantitative variables to characterize the study population. X2 tests or two-sided Fisher test and Student's t-test or Mann-Whitney U-test, were used when appropriate. Clinical cases and summary results: 98 women were evaluated (65 treated with nifedipine capsules and 33 treated with nifedipine oral solution). No differences in gestational age, percentage of rupture of membranes, mean cervical length and cervical dilatation at admission were found between both groups. Rate of previous preterm delivery was similar in both groups too. There were 2 cases in each group in which tocolysis was discontinued because of suspected chorioamnionitis or loss of fetal wellbeing. No statistical differences were found in the need of an alternative tocolytic therapy; neither in the need of rescue doses within the first 6 hours or the total dose of medication received during admission. No differences in gestational age at delivery or perinatal outcomes were observed. The maternal side effects in the nifedipine capsules group were 36,9% and in the nifedipine oral solution were 12.1%, which showed a statistically significant difference (p=0.01). No serious maternal complications were observed in any of both groups. Conclusion: In this retrospective study both nifedipine formulations appear to be equally effective for acute tocolysis. The maternal side effects were higher with nifedipine capsules. (Table Presented).

Database: EMBASE

9. Effectiveness of nifedipine in threatened preterm labor: A randomized trial

Author(s): Songthamwat S.; Na Nan C.; Songthamwat M.

Source: International Journal of Women's Health; Jun 2018; vol. 10 ; p. 317-323

Publication Date: Jun 2018

Publication Type(s): Article

Available at International Journal of Women's Health - from Europe PubMed Central - Open Access

Abstract: Objective: Threatened preterm labor is a condition in which regular uterine contractions occur at least 1 time in 10 minutes and persist for more than 30 minutes before completion of 37 weeks of gestation without dilatation of the cervix. In preterm labor with cervical dilatation, the efficacy of tocolytics was proven for prolonging pregnancy. However, in threatened preterm labor, the efficacy of tocolytics has not yet been well studied. This study aimed to evaluate the effectiveness of nifedipine versus a placebo for inhibiting uterine contraction in threatened preterm labor. Materials and methods: A randomized, double-blinded, placebo-controlled study with 206 threatened preterm labor patients was undertaken. The participants were randomly allocated into either nifedipine or placebo groups. The proportion of patients with successful treatment, gestational age at delivery, and neonatal outcome were compared between the 2 groups. Results: After 90 minutes of treatment, 88.3% of the nifedipine group and 69.9% of the placebo group had no uterine contraction (P<0.001). Nifedipine led to successful treatment outcomes in 77.6% of the total participants compared with 49.5% in the placebo group (P<0.001). The remainder of the participants from both groups needed a second-line tocolytic drug. Of these, 9.7% in the nifedipine group delivered within 48 hours compared with 12.6% in the placebo group (P>0.05). Mean gestation age at delivery and neonatal complications for both groups were not significantly different. Conclusion: Nifedipine had a higher success rate for inhibiting threatened preterm contractions.

Database: EMBASE

10. Effect of maintenance tocolysis with nifedipine in established preterm labour on pregnancy prolongation and neonatal outcome.

Author(s): Aggarwal, Ajay; Bagga, Rashmi; Girish, Bhavana; Kalra, Jaswinder; Kumar, Praveen

Source: Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology; Feb 2018; vol. 38 (no. 2); p. 177-184

Publication Date: Feb 2018

Publication Type(s): Randomized Controlled Trial Journal Article

PubMedID: 28784001

Abstract: Fifty women with singleton pregnancies between 26+0/7 and 33+6/7 weeks of gestation and arrested preterm labour (PTL) after acute tocolysis were randomised by a computer generated randomisation table into an intervention group (n = 25) who received maintenance tocolysis with tablet nifedipine for 12 days or up to 34 weeks of gestation, whichever was later and a control group (n = 25). The primary outcome was achievement of term gestation and the secondary outcomes were the number of days gained till delivery and neonatal mortality and morbidity. The mean gestation at admission, cervical dilatation and effacement were similar in the two groups (30 + weeks, 2.5 cm, 60%). In the intervention group, 7/25 (28%) and in the control group, 2/25 (8%) delivered at term (p = .066) and pregnancy prolongation of 20 days (IQR 2.5-51) and 14 days (IQR 1-27.5) were achieved, respectively (p = .269). Maintenance tocolysis was given for a median of 14 days (range 3-25.5). Kaplan-Meier analysis showed no statistically significant difference in prolongation of pregnancy between the control and the intervention groups (p = .077). The median number of days of neonatal hospital stay were reduced with maintenance tocolysis, but the difference was not significant (4.0 vs 5.5; p = .608). The mean birth weight was significantly higher in the intervention group (2266 vs 1880 g, p = .044). Among women at a high risk for preterm birth (PTB) due to established PTL as evidenced by a mean cervical dilatation of 2.5 cm and a PTB rate of 92% in the control group, maintenance tocolysis did not prolong the pregnancy or reduce the neonatal hospital stay significantly. Impact statement What is already known on this subject: In women with preterm labour (PTL) the role of maintenance tocolysis following acute tocolysis to reduce recurrent PTL is uncertain. Of the six studies using nifedipine, one reported pregnancy prolongation (26.65 vs 16.14 days, p = .007), but similar perinatal outcome (Sayin et al. 2004). Others did not find pregnancy prolongation (Carr et al. 1999 ; Lyell et al. 2008 ; Uma et al. 2012 ; Roos et al. 2013 ; Parry et al. 2014). The PTB rate in the control groups ranged from 38 to 67%. A Cochrane review reported pregnancy prolongation by 5.35 days but similar neonatal outcome (RR 0.75) (Naik et al. 2013). A meta-analysis including five studies using progesterone and five using nifedipine concluded that progesterone, but not nifedipine, prolonged pregnancy (Ding et al. 2016). Thus, data on maintenance tocolysis is limited and inconclusive. What the results of this study add: In the present randomised study in 50 women with arrested PTL, 25 received maintenance tocolysis. The mean gestation at admission, cervical dilatation and effacement were similar in the two groups (30+ weeks, 2.5cm, 60%). In the intervention group, 7/25 (28%) and controls, 2/25 (8%) delivered at term (p = .066) and pregnancy prolongation of 20 days (IQR 2.5-51) and 14 days (IQR 1-27.5) were achieved, respectively (p = .269). Kaplan-Meier analysis showed no statistically significant difference in prolongation of pregnancy between the control and the intervention groups (p = .077). The median number of days of neonatal hospital stay were reduced with maintenance tocolysis but the difference was not significant (4.0 vs 5.5; p = .608). What are the implications of these findings for clinical practice and/or future research: The mean birth weight was higher in the intervention group (2266 vs 1880g, p = .044). Future studies should take cervical dilatation and the PTB rate in the control group into consideration while assessing the impact of maintenance tocolysis.

Database: Medline

11. Maintaining and repeating tocolysis: A reflection on evidence.

Author(s): Dehaene, Isabelle; Bergman, Lina; Turtiainen, Paula; Ridout, Alexandra; Mol, Ben Willem; Lorthe, Elsa; from the International Spontaneous Preterm birth Young Investigators group (I-SPY)

Source: Seminars in perinatology; Dec 2017; vol. 41 (no. 8); p. 468-476

Publication Date: Dec 2017

Publication Type(s): Journal Article Review

PubMedID: 28943054

Abstract: It is inherent to human logic that both doctors and patients want to suppress uterine contractions when a woman presents in threatened preterm labor. Tocolysis is widely applied in women with threatened preterm labor with a variety of drugs. According to literature, tocolysis is indicated to enable transfer to a tertiary center as well as to ensure the administration of corticosteroids for fetal maturation. There is international discrepancy in the content and the implementation of guidelines on preterm labor. Tocolysis is often maintained or repeated. Nevertheless, the benefit of prolonging pregnancy has not yet been proven, and it is not impossible that prolongation of the pregnancy in a potential hostile environment could harm the fetus. Here we reflect on the use of tocolysis, focusing on maintenance and repeated tocolysis, and compare international guidelines and practices to available evidence. Finally, we propose strategies to improve the evaluation and use of tocolytics, with potential implications for future research.

Database: Medline

12. Introducing and auditing a new treatment package for preterm labour using Nifedipine tocolysis protocol in a tertiary maternity hospital

Author(s): Karia A.M.; Verzune M.; Shahin M.M.

Source: BJOG: An International Journal of Obstetrics and Gynaecology; Mar 2017; vol. 124 ; p. 79

Publication Date: Mar 2017

Publication Type(s): Conference Abstract

Available at BJOG: An International Journal of Obstetrics and Gynaecology - from Wiley Online Library

Abstract: Preterm labour affects 5-9% of pregnancies. Outcomes in women with preterm labour can be improved if delivery can be delayed. Several tocolytic agents are suggested with variable success, cost and side effects. Nifedipine can be considered as a tocolytic of choice. In our study we are sharing some difficulties during the development, implementation and auditing a new practice guideline. Developing a local evidence-based guideline for nifedipine use, with the lack of national or international guidance was a challenge. There was a need for an agreed regimen including: form, intake, dosing, administration interval, monitoring, success threshold, indications for switching to second line tocolytic, and selection of maintenance dose. We did a prospective audit for all patients presented with preterm labour, and were suitable for tocolysis. Data collected for gestational age, place for tocolysis, use of steroids, magnesium sulphate, antibiotics, first and second line tocolytic, nifedipine protocol, maternal and neonatal outcome and gestational age at delivery. Our audit included 21 women with preterm and threatened preterm labour in our hospital. All patients were immediately transfer to labour ward. 19% delivered in 24 hours, the rest delivered at term. Atosiban was started in 12.5% of patients. All patients had tocolysis initiated although 18.7% patients found to have cervical dilatation >4 cm. 87.5% patients had steroids administered. Implementing a new tocolysis guideline for preterm labour can be successful with careful guideline development, implementation planning and auditing change of practice, with resultant good outcomes and cost savings.

Database: EMBASE

13. Nifedipine maintenance tocolysis and perinatal outcome: an individual participant data meta-analysis.

Author(s): van Vliet, Eog; Dijkema, G H; Schuit, E; Heida, K Y; Roos, C; van der Post, Jam; Parry, E C; McCowan, L; Lyell, D J; El-Sayed, Y Y; Carr, D B; Clark, A L; Mahdy, Z A; Uma, M; Sayin, N C; Varol, G F; Mol, B W; Oudijk, M A

Source: BJOG : an international journal of obstetrics and gynaecology; Oct 2016; vol. 123 (no. 11); p. 1753-1760

Publication Date: Oct 2016

Publication Type(s): Meta-analysis Journal Article Review

PubMedID: 27550838

Abstract:BACKGROUNDPreterm birth is the leading cause of neonatal mortality and morbidity in developed countries. Whether continued tocolysis after 48 hours of rescue tocolysis improves neonatal outcome is unproven.OBJECTIVESTo evaluate the effectiveness of maintenance tocolytic therapy with oral nifedipine on the reduction of adverse neonatal outcomes and the prolongation of pregnancy by performing an individual patient data meta-analysis (IPDMA).SEARCH STRATEGYWe searched PubMed, Embase, and Cochrane databases for randomised controlled trials of maintenance tocolysis therapy with nifedipine in preterm labour.SELECTION CRITERIAWe selected trials including pregnant women between 24 and 36(6/7) weeks of gestation (gestational age, GA) with imminent preterm labour who had not delivered after 48 hours of initial tocolysis, and compared maintenance nifedipine tocolysis with placebo/no treatment.DATA COLLECTION AND ANALYSISThe primary outcome was perinatal mortality. Secondary outcome measures were intraventricular haemorrhage (IVH), necrotising enterocolitis (NEC), infant respiratory distress syndrome (IRDS), prolongation of pregnancy, GA at delivery, birthweight, neonatal intensive care unit admission, and number of days on ventilation support. Pre-specified subgroup analyses were performed.MAIN RESULTSSix randomised controlled trials were included in this IPDMA, encompassing data from 787 patients (n = 390 for nifedipine; n = 397 for placebo/no treatment). There was no difference between the groups for the incidence of perinatal death (risk ratio, RR 1.36; 95% confidence interval, 95% CI 0.35-5.33), intraventricular haemorrhage (IVH) ≥ grade II (RR 0.65; 95% CI 0.16-2.67), necrotising enterocolitis (NEC) (RR 1.15; 95% CI 0.50-2.65), infant respiratory distress syndrome (IRDS) (RR 0.98; 95% CI 0.51-1.85), and prolongation of pregnancy (hazard ratio, HR 0.74; 95% CI 0.55-1.01).CONCLUSIONMaintenance tocolysis is not associated with improved perinatal outcome and is therefore not recommended for routine practice.TWEETABLE ABSTRACTNifedipine maintenance tocolysis is not associated with improved perinatal outcome or pregnancy prolongation.

Database: Medline

14. Maintenance tocolysis in preterm labour with nifedipine

Author(s): Aggarwal A.; Bagga R.; Kalra J.; Kumar P.

Source: BJOG: An International Journal of Obstetrics and Gynaecology; Apr 2015; vol. 122 ; p. 157-158

Publication Date: Apr 2015

Publication Type(s): Conference Abstract

Available at BJOG: An International Journal of Obstetrics and Gynaecology - from Wiley Online Library

Available at BJOG: An International Journal of Obstetrics and Gynaecology - from Unpaywall

Abstract: Introduction Preterm birth is the most important determinant of neonatal morbidity and mortality worldwide. Spontaneous preterm labour is the commonest cause of preterm birth and maintenance tocolysis is intended to reduce the incidence of preterm birth. Methods From 2011 to 2012, fifty women with arrested preterm labour between 26+0/7 weeks and 33+6/7 weeks gestation, singleton pregnancy, intact membranes, were enrolled. Tablet nifedipine (plain) was used for acute tocolysis for 48 hours in these women. They were randomised into two groups after successful acute tocolysis. Women in the study group (n = 25) received maintenance tocolysis with tablet nifedipine (retard) 20 mg 8 hourly PO for 12 more days. Women, who did not achieve 34 weeks of gestation after 12 days, continued nifedipine till 34 weeks of gestation. The control group (n = 25) did not receive maintenance tocolysis. The primary outcome was achievement of term gestation; others were number of days gained from initiation of maintenance tocolysis to delivery (latency) and adverse perinatal outcomes. Results Mean gestation at admission was 30+4/7 weeks for study group and 30+6/7 weeks for control (P = 0.582, NS). Median cervical dilatation and effacement was 2.5 cm (IQR 2.5-3.5) and 60% for the two groups. In the study group 7/25 (28%) women while 2/25 (8%) women in the control group, delivered at term (P = 0.066). A latency of 20 (IQR 2.5-51) days versus 14 (IQR 1-27.5) days was achieved for study and control group, respectively (P = 0.269, NS). Kaplan-Meier analysis showed a positive trend for pregnancy prolongation in the study group (P = 0.077). A significantly increased mean birthweight of babies born in study group (2266 versus 1880 g in controls, P = 0.044) was observed. A trend towards less number of days of hospital stay for babies in study group (median days 4; IQR 2-10 versus 5.5; IQR 2.25-12 in control) and neonatal care (median days 4; IQR 2.25-39 versus 7; IQR 4.75-17.75 in control) was seen. Conclusion The beneficial trends of maintenance tocolysis observed in the present study need to be confirmed by a larger study, as the chief limitation of the present study is a small sample size. We observed that selection of women who require tocolysis is important as the present study is the only one with higher number of women in the control group who delivered preterm actually. Women with true preterm labour and clinically evident cervical changes are more likely to deliver preterm and may benefit more with acute tocolysis followed by maintenance tocolysis.

Database: EMBASE

15. Tocolysis for preterm labor: Expert opinion

Author(s): Hosli I.; Sperschneider C.; Drack G.; Zimmermann R.; Surbek D.; Irion O.

Source: Archives of Gynecology and Obstetrics; 2014; vol. 289 (no. 4); p. 903-909

Publication Date: 2014

Publication Type(s): Article

PubMedID: 24385286

Available at Archives of Gynecology and Obstetrics - from SpringerLink - Medicine

Available at Archives of Gynecology and Obstetrics - from Unpaywall

Abstract: Tocolysis is an important treatment in the improvement of outcome in preterm labor and preterm birth, provided that its use follows clear evidence-based recommendations. In this expert opinion, the most recent evidence about efficacy and side effects of different tocolytics is being reviewed and evidence-based recommendation about diagnosis and treatment of preterm labor is given. Further aspects such as progesterone administration or antibiotic treatment for the prevention of preterm birth are included. Our review demonstrates that an individualized choice of different tocolytics and additional treatments is necessary to improve short- and long-term neonatal outcome in preterm labor and preterm birth. © 2014 Springer-Verlag.

Database: EMBASE

16. Prophylactic oral nifedipine to reduce preterm delivery: a randomized controlled trial in women at high risk.

Author(s): Danti, Luana; Zonca, Marina; Barbetti, Lorena; Lojacono, Andrea; Marini, Silvia; Cappello, Nazario; Bianchi, Umberto; Benedetto, Chiara

Source: Acta obstetricia et gynecologica Scandinavica; Aug 2014; vol. 93 (no. 8); p. 802-808

Publication Date: Aug 2014

Publication Type(s): Research Support, Non-u.s. Gov't Randomized Controlled Trial Multicenter Study Journal Article

PubMedID: 24773243

Available at Acta obstetricia et gynecologica Scandinavica - from Wiley Online Library

Abstract:OBJECTIVETo establish the efficacy of prophylactic nifedipine vs. placebo in reducing spontaneous preterm delivery in asymptomatic women at high risk for preterm delivery.DESIGNProspective multicentric randomized double-blind study.SETTINGTertiary care centre, University Hospitals of Brescia and Torino, Italy.POPULATIONEighty-seven singleton pregnancies without uterine contractions and ultrasonographic cervical length of ≤25 mm at 24-32 weeks, at risk for preterm delivery, with longitudinal follow up in our Preterm Prevention Clinic.METHODSSelection was done on the basis of ultrasonographic cervical length; 43 women were randomized to receive placebo and 44 to receive nifedipine.MAIN OUTCOME MEASURESPrimary end point: spontaneous preterm delivery <37 weeks in nifedipine vs. placebo.SECONDARY OUTCOMESdelivery <32 weeks, maternal side effects, neonatal complications, admissions to the Neonatal Intensive Care Unit and randomization/delivery time in nifedipine vs. placebo.RESULTSThere was no trend towards a lower risk of spontaneous preterm delivery, neither at <37 weeks of nifedipine vs. placebo (11.4% vs. 19.0%; p = 0.320), or <32 weeks (2.3% vs. 2.4%; p = 0.973). Nifedipine reduced spontaneous preterm delivery <37 weeks (p = 0.015) in the multiparous women by stratified analysis for parity. SECONDARY OUTCOMES between the groups did not differ except for a higher percentage of maternal side-effects in the nifedipine group (31.8%) vs. placebo (11.9%) (p < 0.05). Subgroup analysis showed a borderline (p = 0.047) lower percentage of spontaneous preterm delivery in women with a ultrasonographic cervical length of <20 mm in the

nifedipine group.CONCLUSIONSProphylactic nifedipine in asymptomatic women at high risk for preterm delivery had a positive effect on the rate of spontaneous preterm delivery <37 weeks in multiparous women.

Database: Medline

17. The NIFTY study: A multicentre randomised double-blind placebo-controlled trial of nifedipine maintenance tocolysis in fetal fibronectin-positive women in threatened preterm labour

Author(s): Parry E.; Stone P.; McCowen L.; Roos C.; Hayward L.; Mol B.W.

Source: Australian and New Zealand Journal of Obstetrics and Gynaecology; Jun 2014; vol. 54 (no. 3); p. 231-236

Publication Date: Jun 2014

Publication Type(s): Article

PubMedID: 24506318

Abstract: Objective In an unselected group of women with signs of preterm labour, maintenance tocolysis is not effective in the prevention of preterm birth and does not improve neonatal outcome. Among women with signs of preterm labour, those who are fetal fibronectin positive have an increased risk of preterm birth. We investigated whether maintenance tocolysis with nifedipine would delay delivery and improve neonatal outcome in women with threatened preterm labour and a positive fetal fibronectin status. Study Design Women with a singleton pregnancy in threatened preterm labour (24+0 to 33+6 weeks) with a positive fetal fibronectin test were randomised to nifedipine or placebo. Study medication was continued until 36 completed weeks' gestation. The primary endpoint was prolongation of pregnancy of seven days. Secondary endpoints were gestational age at delivery and length of NICU admission. Results Of the 60 participants, 29 received nifedipine and 31 placebo. Prolongation of pregnancy by >7 days occurred in 22/29 (76%) in the nifedipine group and 25/31 (81%) in the placebo group (relative risks, RR 0.94 [0.72-1.2]). Gestational age at delivery was 36.1 +/- 5.1 weeks for nifedipine and 36.8 +/- 3.6 weeks for placebo (P = 0.027). Length of NICU admission [median (interquartile ranges, IQR)] was 27 (24-41) days and 16 (8-37) days in nifedipine and placebo groups, respectively (P = 0.17). Conclusion In women with threatened preterm labour who are fetal fibronectin positive, maintenance tocolysis with nifedipine does not seem to prolong pregnancy, nor reduce length of NICU admission. © 2014 The Royal Australian and New Zealand College of Obstetricians and Gynaecologists.

Database: EMBASE

18. Calcium channel blockers as tocolytics: Principles of their actions, adverse effects and therapeutic combinations

Author(s): Gaspar R.; Hajagos-Toth J.

Source: Pharmaceuticals; 2013; vol. 6 (no. 6); p. 689-699

Publication Date: 2013

Publication Type(s): Review

Abstract: Dihydropyridine Ca2+ channel blockers (CCBs) are widely accepted in the treatment of premature labour. Their mechanism of action in tocolysis involves the blockade of L-type Ca2+ channels, influenced by the Ca2+-activated K+ channels, beta-adrenergic receptors (beta-ARs) and sexual hormones. In clinical practice, most experience has been gained with the use of nifedipine, whose efficacy is superior or comparable to those of beta-agonists and oxytocin antagonists. Additionally, it has a favourable adverse effect profile as compared with the majority of other tocolytics. The most frequent and well-tolerated side-effects of CCBs are tachycardia, headache and hypotension. In tocolytic therapy efforts are currently being made to find combinations of tocolytic agents that yield better therapeutic action. The available human and animal studies suggest that the combination of CCBs with beta-AR agonists is beneficial, although such combinations can pose risk of pulmonary oedema in multiple pregnancies and maternal cardiovascular diseases. Preclinical data indicate the potential benefit of combinations of CCBs and oxytocin antagonists. However, the combinations of CCBs with progesterone or cyclooxygenase inhibitors may decrease their efficacy. The CCBs are likely to remain one of the most important groups of drugs for the rapid inhibition of premature uterine contractions. Their significance may be magnified by further clinical studies on their combined use for tocolysis. © 2013 by the authors; licensee MDPI, Basel, Switzerland.

Database: EMBASE

19. Nifedipine pharmacokinetics are influenced by CYP3A5 genotype when used as a preterm labor tocolytic

Author(s): Haas D.M.; Quinney S.K.; Clay J.M.; Renbarger J.L.; Hebert M.F.; Clark S.; Umans J.G.; Caritis S.N.

Source: American Journal of Perinatology; 2013; vol. 30 (no. 4); p. 275-282

Publication Date: 2013

Publication Type(s): Article

PubMedID: 22875663

Abstract: Objective To characterize the pharmacokinetics and pharmacogenetics of nifedipine in pregnancy. Study Design Pregnant women receiving oral nifedipine underwent steady-state pharmacokinetic testing over one dosing interval. DNA was obtained and genotyped for cytochrome P450 (CYP) 3A5 and CYP3A4*1B. Nifedipine and oxidized nifedipine concentrations were measured in plasma, and pharmacokinetic parameters were compared between those women who expressed a CYP3A5*1 allele and those who expressed only variant CYP3A5 alleles (*3, *6, or *7). Results Fourteen women had complete data to analyze. Four women (29%) expressed variant CYP3A5; three of these women were also CYP3A4*1B allele carriers. The mean half-life of nifedipine was 1.68 +/- 1.56 hours. The area under the curve from 0 to 6 hours for the women receiving nifedipine every 6 hours was 207 +/- 138 mug.h /L. Oral clearance was different between high expressers and low expressers (232.0 +/- 37.8 mug/mL versus 85.6 +/- 45.0 mug/mL, respectively; p = 0.007). Conclusion CYP3A5 genotype influences the oral clearance of nifedipine in pregnant women.

Database: EMBASE

20. 48-Hours administration of nifedipine in spontaneous preterm labor - Doppler blood flow assessment of placental and fetal circulation

Author(s): Grzesiak M.; Wilczynski J.; Ahmed R.B.

Source: Neuroendocrinology Letters; 2013; vol. 34 (no. 7); p. 687-692

Publication Date: 2013

Publication Type(s): Article

PubMedID: 24463995

Abstract:OBJECTIVES: The aims were to assess the placental and fetal circulation during nifedipine tocolysis within the first 48 hours of therapy. METHODS: Placental and fetal circulation was assessed in Doppler ultrasound examination prior to nifedipine administration and then after 24 and 48 hours. Maternal heart rate and PI in uterine arteries were evaluated as well as FHR, RI and PI of UA and MCA. E/A-wave ratio for A-V valves, MPI and SF were calculated for both ventricles independently. To determine changes over time in all study variable analysis of variance (ANOVA) for repeated measurements followed by Tukey-Kramer's multiple comparison test was used. The effects of additional clinical covariates were checked. RESULTS: Uterine and umbilical blood flow patterns were not altered significantly during administration of nifedypine tocolysis. While MCA Doppler indicies such as RI and PI were unchanged, the evaluation of MCA PSV revealed a transient significant decrease after 24 hours. A resolution of this distraction was observed within the following 24 hours. No significant changes were observed in direct fetal cardiac function parameters calculated separately for both ventricles. CONCLUSIONS: The decrease of MCA PSV after 24 hours of treatment was isolated and transient hemodynamic distraction observed during treatment. Neither fetal cardiac parameters nor other Doppler indices were changed. Therefore oral administration of nifedipine seems not to alter uterine nor fetal arterial blood flow pattern seriously. As significant changes were observed by different authors, further studies should be performed to verify the optimal total dose of nifedipine and its influence on hemodynamic conditions. ©2013 Neuroendocrinology Letters.

Database: EMBASE

21. Effect of maintenance tocolysis with nifedipine in threatened preterm labor on perinatal outcomes: a randomized controlled trial.

Author(s): Roos, Carolien; Spaanderman, Marc E A; Schuit, Ewoud; Bloemenkamp, Kitty W M; Bolte, Antoinette C; Cornette, Jérôme; Duvekot, Johannes J J; van Eyck, Jim; Franssen, Maureen T M; de Groot, Christianne J; Kok, Joke H; Kwee, Anneke; Merién, Ashley; Nij Bijvank, Bas; Opmeer, Brent C; Oudijk, Martijn A; van Pampus, Mariëlle G; Papatsonis, Dimitri N M; Porath, Martina M; Scheepers, Hubertina C J; Scherjon, Sicco A; Sollie, Krystyna M; Vijgen, Sylvia M C; Willekes, Christine; Mol, Ben Willem J; van der Post, Joris A M; Lotgering, Fred K; APOSTEL-II Study Group

Source: JAMA; Jan 2013; vol. 309 (no. 1); p. 41-47

Publication Date: Jan 2013

Publication Type(s): Research Support, Non-u.s. Gov't Randomized Controlled Trial Multicenter Study Journal Article

PubMedID: 23280223

Available at JAMA - from Unpaywall

Abstract:IMPORTANCEIn threatened preterm labor, maintenance tocolysis with nifedipine, after an initial course of tocolysis and corticosteroids for 48 hours, may improve perinatal outcome.OBJECTIVETo determine whether maintenance tocolysis with nifedipine will reduce adverse perinatal outcomes due to premature birth.DESIGN, SETTING, AND PARTICIPANTSAPOSTEL-II (Assessment of Perinatal Outcome with Sustained Tocolysis in Early Labor) is a double-blind, placebo-controlled trial performed in 11 perinatal units including all tertiary centers in The Netherlands. From June 2008 to February 2010, women with threatened preterm labor between 26 weeks (plus 0 days) and 32 weeks (plus 2 days) gestation, who had not delivered after 48 hours of tocolysis and a completed course of corticosteroids, were enrolled. Surviving infants were followed up until 6 months after birth (ended August 2010).INTERVENTIONRandomization assigned 406 women to maintenance tocolysis with nifedipine orally (80 mg/d; n = 201) or placebo (n = 205) for 12 days. Assigned treatment was masked from investigators, participants, clinicians, and research nurses.MAIN OUTCOME MEASURESPrimary outcome was a composite of adverse perinatal outcomes (perinatal death, chronic lung disease, neonatal sepsis, intraventricular hemorrhage >grade 2, periventricular leukomalacia >grade 1, or necrotizing enterocolitis). Analyses were completed on an intention-to-treat basis.RESULTSMean (SD) gestational age at randomization was 29.2 (1.7) weeks for both groups. Adverse perinatal outcome was not significantly different between groups: 11.9% (24/201; 95% CI, 7.5%-16.4%) for nifedipine vs 13.7% (28/205; 95% CI, 9.0%-18.4%) for placebo (relative risk, 0.87; 95% CI, 0.53-1.45).CONCLUSIONS AND RELEVANCEIn patients with threatened preterm labor, nifedipine-maintained tocolysis did not result in a statistically significant reduction in adverse perinatal outcomes when compared with placebo. Although the lower than anticipated rate of adverse perinatal outcomes in the control group indicates that a benefit of nifedipine cannot completely be excluded, its use for maintenance tocolysis does not appear beneficial at this time.TRIAL REGISTRATIONtrialregister.nl Identifier: NTR1336.

Database: Medline

22. Is maintenance tocolysis with nifedipine effective in the reduction of adverse perinatal outcome: An individual participant data meta-analysis

Author(s): Heida K.; Oudijk M.; Roos C.; Schuit E.; Lyell D.; El-Sayed Y.; Parry E.; McCowan L.; Mol B.W.

Source: American Journal of Obstetrics and Gynecology; Jan 2013; vol. 208 (no. 1)

Publication Date: Jan 2013

Publication Type(s): Conference Abstract

Abstract:OBJECTIVE: Preterm birth is the main cause of adverse perinatal outcome in the western world. Randomized controlled trials ofnifedipine maintenance tocolysis in patients with threatened preterm labor have shown no clear benefit on perinatal outcome and contradicting results of prolongation of pregnancy. Our objective was to combine different randomized trials in an individual patient data meta-analysis to evaluate the effect of maintenance tocolysis on perinatal outcome. STUDY DESIGN: We performed an individual participant data metaanalysis of randomized trials on nifedipine maintenance tocolysis. We searched for studies on pregnant patients between 24 and 34 weeks of gestation with threatened preterm labor who had not delivered after tocolysis for 48 hours. We added the data of the individual trials in one dataset. Primary outcome was adverse perinatal outcome, defined as a composite of perinatal death, infant respiratory distress syndrome, necrotizing enterocolitis and intraventricular hemorrhage > grade 2. Secondary outcomes included gestational age at delivery and prolongation of pregnancy. RESULTS: We identified 3 double-blind, placebo-controlled trials, that included 522 patients with 638 children, of which 254 patients had been allocated to nifedipine and 268 to placebo. Baseline characteristics in both groups were comparable. Adverse perinatal outcome was not significantly different between the two groups: 13.4 % in the nifedipine group and 12.6 % in the placebo group (RR 1.0; 95% CI 0.65-1.7). Gestational age at delivery was comparable for both groups;. median prolongation of pregnancy was 31 (10.3-57) and 36 (9.8-60) days in the nifedipine and placebo group, respectively (HR 0.98; 95% CI 0.83-1.2). Mean length of neonatal intensive care unit admission was comparable. CONCLUSION: After successful tocolysis in patients with threatened preterm labor, maintenance tocolysis is ineffective in reducing adverse perinatal outcome and in prolonging pregnancy.

Database: EMBASE

23. A Semi-Mechanistic Metabolism Model of CYP3A Substrates in Pregnancy: Predicting Changes in Midazolam and Nifedipine Pharmacokinetics.

Author(s): Quinney, S K; Mohamed, A N; Hebert, M F; Haas, D M; Clark, S; Umans, J G; Caritis, S N; Li, L

Source: CPT: pharmacometrics & systems pharmacology; Sep 2012; vol. 1 ; p. e2

Publication Date: Sep 2012

Publication Type(s): Journal Article

PubMedID: 23835882

Available at CPT: pharmacometrics & systems pharmacology - from Europe PubMed Central - Open Access

Available at CPT: pharmacometrics & systems pharmacology - from Unpaywall

Abstract: Physiological changes in pregnancy, including changes in body composition and metabolic enzyme activity, can alter drug pharmacokinetics. A semi-mechanistic metabolism model was developed to describe the pharmacokinetics of two cytochrome P450 3A (CYP3A) substrates, midazolam and nifedipine, in obstetrics patients. The model parameters were optimized to fit the data of oral midazolam pharmacokinetics in pregnant women, by increasing CYP3A-induced hepatic metabolism 1.6-fold in the model with no change in gut wall metabolism. Fetal metabolism had a negligible effect on maternal plasma drug concentrations. Validation of the model was performed by applying changes in volume of distribution and metabolism, consistent with those observed for midazolam, to the pharmacokinetics parameters of immediate-release nifedipine in healthy volunteers. The predicted steady-state areas under the concentration-time curve (AUCs) for nifedipine were within 15% of the data observed in pregnant women undergoing treatment for preterm labor. This model predicts the pharmacokinetics of two CYP3A substrates in pregnancy, and may be applicable to other CYP3A substrates as well.CPT: Pharmacometrics & Systems Pharmacology (2012) 1, e2; doi:10.1038/psp.2012.5; advance online publication 26 September 2012.

Database: Medline

24. Maintenance nifedipine for tocolysis in preterm labour: A prospective randomised controlled trial

Author(s): Uma M.; Ixora K.A.; Nor Azlin M.I.; Mahdy Z.A.

Source: BJOG: An International Journal of Obstetrics and Gynaecology; Jun 2012; vol. 119 ; p. 35-36

Publication Date: Jun 2012

Publication Type(s): Conference Abstract

Available at BJOG: An International Journal of Obstetrics and Gynaecology - from Wiley Online Library

Abstract: Objective: (i) To compare the incidence of preterm delivery in patients treated with or without maintenance nifedipine. (ii) To compare the incidence of recurrent preterm contractions in patients treated with or without maintenance nifedipine. Methods: This is a prospective randomised controlled trial of 98 women experiencing preterm labour from January 2010 until August 2011. Women with preterm labour at 22-34 weeks were randomised to receive either standard dose of tocolysis with nifedipine (control group: T. Nifedipine 20 mg 1/2 hourly x 3 doses, then 20 mg tds for 72 h) or maintenance nifedipine up to 36 weeks (treatment group: T. Nifedipine as per control group, then 20 mg tds continued up to 36 weeks). Both groups were compared in terms of preterm delivery, perinatal outcomes and maternal side effects of nifedipine. Result: The treatment group had a significant prolongation of pregnancy, with the mean gestational age at delivery being 36.92 +/- 2.24 vs. 35.59 +/- 2.82 in the control group. There were more term deliveries after 37 weeks in

the treatment group, 60% vs. 40% in the control group, however this was not statistically significant. There was no significant difference in the occurrence of recurrent preterm labour between the groups. Conclusion: This study concurred with recent trials and metaanalyses, which showed no benefit of maintenance tocolytic therapy with nifedipine with regards to episodes of recurrent preterm labour and adverse neonatal outcomes. Although there was significant prolongation of pregnancy (of about 9 days) with maintenance nifedipine, this may not be clinically significant as neonatal morbidity rates are low in gestation >=34 weeks.

Database: EMBASE

25. A pilot study of the impact of genotype on nifedipine pharmacokinetics when used as a tocolytic

Author(s): Haas D.M.; Quinney S.K.; McCormick C.L.; Jones D.R.; Renbarger J.L.

Source: Journal of Maternal-Fetal and Neonatal Medicine; Apr 2012; vol. 25 (no. 4); p. 419-423

Publication Date: Apr 2012

Publication Type(s): Article

PubMedID: 21644845

Abstract: Objective.To characterize the pharmacokinetics of nifedipine when used for tocolysis in preterm labor and to determine the impact of genetics on these parameters. Study design.Pharmacokinetic study performed on women given tocolytic nifedipine. Over one dosing interval, drug concentrations, clinical data, and genotype for Cytochrome P450 (CYP)3A5 polymorphisms were obtained. Non-compartmental pharmacokinetic analysis was used to estimate nifedipine exposure at steady state. Results.The mean nifedipine area under the curve in 20 pregnant women was 86.1+/-61.1 ng/ml/h. The mean nifedipine exposure differed by expression of CYP3A5 (expressers [exp]: 139.5+/-97.3 ng/ml/h vs. nonexpressers[non]: 68.3 +/- 31.8 ng/ml/h, p = 0.02). Four women consumed CYP3A inhibitors and this affected the nifedipine concentrations (p < 0.001). CYP3A5 expressers had less improvement in contraction frequency after the loading dose (p = 0.04), at steady state (p = 0.006), and at 0-1 h after the study dose (p < 0.001). Conclusions.CYP3A5 genotype plays a role in nifedipine concentration when used as a tocolytic.

Database: EMBASE

26. Compartmental pharmacokinetics (PK) of immediate release nifedipine (NIF) in pregnancy: Variability in absorption

Author(s): Nader A.M.; Caritis S.N.; Hebert M.F.; Clark S.M.; Flockhart D.A.; Quinney S.K.

Source: Clinical Pharmacology and Therapeutics; Mar 2012; vol. 91

Publication Date: Mar 2012

Publication Type(s): Conference Abstract

Abstract:BACKGROUND: NIF is used for treatment of hypertension and preterm labor. A few small studies report NIF plasma concentrations (conc.) in pregnancy, but most have not performed full PK analyses, and none reported compartmental PK. The objective of this study was to determine NIF PK parameters in pregnancy using compartmental models. METHODS: NIF conc. were available from 13 pregnant women taking part in the OPRU under-studied drugs in pregnancy study. Steady-state blood samples were obtained over one dosing interval in subjects taking 10 or 20 mg immediate release NIF. Individual and population PK modeling was performed. Results were compared between the 2 methods to determine the ability of a population PK model to describe NIF absorption in all subjects. Modeling procedures and plots were done in NONMEM VII and R. RESULTS: A 2-compartment linear PK model with first-order elimination and absorption best described the observed NIF conc. but was unable to describe absorption for most subjects. A mixture model for absorption identified 2 subpopulations with absorption rate constants (Ka) and lag times of 0.56 hr-1 /0.42 hr (n=4) and 14.5 hr-1 /0.12 hr (n=9). Absorption phase and Cmax were not accurately described for 6 subjects. Fitting individual subjects separately accurately described absorption phase and Cmax and resulted in median Ka and tlag (6 subjects) of 4.7 hr-1 (0.64-10.7) and 0.45 hrs (0.22-0.95), respectively. Population estimate of NIF CL was 81 L/hr, similar to the median CL (79 L/hr) obtained from individual fitting. CONCLUSION: A population mixture model for absorption was needed to describe NIF absorption profile in pregnancy, although it fails to assign all subjects to correct absorption rates and lag times. Individual fitting better describes observed conc. and shows a wide range of absorption rates and lag time between the 13 subjects. Future prospective studies are needed to define factors contributing to interindividual variability in NIF absorption.

Database: EMBASE

27. Nifedipine in the management of preterm labor: a systematic review and metaanalysis.

Author(s): Conde-Agudelo, Agustín; Romero, Roberto; Kusanovic, Juan Pedro

Source: American journal of obstetrics and gynecology; Feb 2011; vol. 204 (no. 2); p. 134

Publication Date: Feb 2011

Publication Type(s): Meta-analysis Research Support, N.i.h., Intramural Journal Article Review Systematic Review

PubMedID: 21284967

Abstract:OBJECTIVETo determine the efficacy and safety of nifedipine as a tocolytic agent in women with preterm labor.STUDY DESIGNA systematic review and metaanalysis of randomized controlled trials.RESULTSTwenty-six trials (2179 women) were included. Nifedipine was associated with a significant reduction in the risk of delivery within 7 days of initiation of treatment and before 34 weeks' gestation, respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, neonatal jaundice, and admission to the neonatal intensive care unit when compared with β_2-adrenergic-receptor agonists. There was no difference between nifedipine and magnesium sulfate in tocolytic efficacy. Nifedipine was associated with significantly fewer maternal adverse events than β_2-adrenergic-receptor agonists and magnesium sulfate. Maintenance nifedipine

tocolysis was ineffective in prolonging gestation or improving neonatal outcomes when compared with placebo or no treatment.CONCLUSIONNifedipine is superior to β_2-adrenergic-receptor agonists and magnesium sulfate for tocolysis in women with preterm labor.

Database: Medline

28. Assessment of perinatal outcome after sustained tocolysis in early labour (APOSTEL-II trial)

Author(s): Roos C.; Spaanderman M.E.A.; Lotgering F.K.; Scheepers L.H.C.J.; Willekes C.; Bloemenkamp K.W.M.; Scherjon S.A.; Bolte A.; Cornette J.; Duvekot H.J.J.; Derks J.B.; Kwee A.; van Eyck J.; Kok J.H.; Merien A.; Porath M.M.; Opmeer B.C.; van Pampus M.G.; Sollie K.; Papatsonis D.N.M.; van der Post J.A.M.; Vijgen S.M.C.; Mol B.W.J.

Source: BMC Pregnancy and Childbirth; Sep 2009; vol. 9 ; p. 42

Publication Date: Sep 2009

Publication Type(s): Article

PubMedID: 19737426

Abstract: Background: Preterm labour is the main cause of perinatal morbidity and mortality in the Western world. At present, there is evidence that tocolysis for 48 hours is useful in women with threatened preterm labour at least before 32 weeks. This allows transfer of the patient to a perinatal centre, and maximizes the effect of corticosteroids for improved neonatal survival. It is questionable whether treatment with tocolytics should be maintained after 48 hours. Methods/Design: The APOSTEL II trial is a multicentre placebo-controlled study. Pregnant women admitted for threatened preterm labour who have been treated with 48 hours corticosteroids and tocolysis will be eligible to participate in the trial between 26+0 and 32+2 weeks gestational age. They will be randomly allocated to nifedipine (intervention) or placebo (control) for twelve days or until delivery, whatever comes first. Discussion: Primary outcome is a composite of perinatal death, and severe neonatal morbidity up to evaluation at 6 months after birth. Secondary outcomes are gestational age at delivery, number of days in neonatal intensive care and total days of the first 6 months out of hospital. In addition a cost-effectiveness analysis will be performed. Analysis will be by intention to treat. The power calculation is based on an expected 11% difference in adverse neonatal outcome. This implies that 406 women have to be randomised (two sided test, beta 0.2 at alpha 0.05). Trial Registration: This trial will provide evidence as to whether maintenance tocolysis reduces severe perinatal morbidity and mortality in women with threatened preterm labour before 32 weeks. Clinical trial registration: http://www.trialregister.nl, NTR 1336, date of registration: June 3rd 2008.

Database: EMBASE

29. Maintenance nifedipine tocolysis compared with placebo: A randomized controlled trial

Author(s): Lyell D.J.; Pullen K.M.; Mannan J.; Chitkara U.; Druzin M.L.; Caughey A.B.; El-Sayed Y.Y.

Source: Obstetrics and Gynecology; Dec 2008; vol. 112 (no. 6); p. 1221-1226

Publication Date: Dec 2008

Publication Type(s): Article

PubMedID: 19037029

Abstract:OBJECTIVE:: To estimate whether maintenance nifedipine tocolysis after arrested preterm labor prolongs pregnancy and improves neonatal outcomes. METHODS:: A prospective, randomized double-blind, multicenter study was conducted. After successful tocolysis, patients were randomly assigned to receive 20 mg nifedipine or an identical-appearing placebo every 4-6 hours until 37 weeks of gestation. The primary outcome was attainment of 37 weeks of gestation. Patients were enrolled between 24 weeks and 34 weeks if they had six or fewer contractions per hour, intact membranes, and less than 4 cm cervical dilation. Exclusion criteria were placental abruption or previa, fetal anomaly incompatible with life, or maternal medical contraindication to tocolysis. Sixty-six patients were required for 80% power to detect a 50% reduction in birth before 37 weeks, with a two-tailed alpha of 0.05. Data were analyzed by intent to treat. RESULTS:: Seventy-one patients were randomly assigned. Two patients were excluded after randomization and one was lost to follow-up. Thirty-five patients received placebo, and 33 received nifedipine. There were no maternal demographic differences between groups; the placebo group was significantly more dilated and effaced at study entry. There was no difference in attainment of 37 weeks (39% nifedipine compared with 37% placebo, P>.91), mean delay of delivery (33.5+/-19.9 days nifedipine compared with 32.6+/-21.4 days placebo, P=.81) or delay of delivery for greater than 48 hours or 1, 2, 3, or 4 weeks. Neonatal outcomes were similar between groups. CONCLUSION:: When compared with placebo, maintenance nifedipine tocolysis did not confer a large reduction in preterm birth or improvement in neonatal outcomes. © 2008 by The American College of Obstetricians and Gynecologists.

Database: EMBASE

30. Pharmacokinetics of tocolytic agents

Author(s): Tsatsaris V.; Cabrol D.; Carbonne B.

Source: Clinical Pharmacokinetics; 2004; vol. 43 (no. 13); p. 833-844

Publication Date: 2004

Publication Type(s): Review

PubMedID: 15509182

Available at Clinical Pharmacokinetics - from SpringerLink - Medicine

Abstract: Tocolytic agents are drugs designed to inhibit contractions of myometrial smooth muscle cells. Such an effect has been demonstrated in vitro or in vivo for several pharmacological agents, including beta-adrenergic agonists, calcium channel antagonists, oxytocin antagonists, NSAIDs and magnesium sulfate. However, the aim of tocolysis is not only to stop uterine contractions or to prevent preterm delivery, but to prevent perinatal morbidity and mortality associated with preterm birth. The achievement of this goal has not yet been clearly demonstrated for any of the drugs available, and the use of tocolytic agents may appear controversial. Therefore, it is important to avoid maternal and fetal toxicity when tocolytic agents are used. During pregnancy, all steps of drug pharmacokinetics are altered. Absorption of drugs administered orally is limited because of delayed stomach emptying and reduced intestinal motility. The volume of distribution of drugs is increased. The metabolic activity of the liver is increased, accelerating the metabolism of lipophilic drugs. Renal filtration is increased, leading to enhanced renal elimination of water-soluble drugs. These modifications are generally responsible for reduced plasma concentration and reduced half-life of most drugs. These specific modifications have to be taken into account when using a drug in pregnant women. The aim of this review is to provide the reader with pharmacological data about drugs currently used to treat preterm labour. Such data in pregnant women may affect the choice of optimal drug dosage and route of administration.

Database: EMBASE

31. Oral nifedipine maintenance therapy after acute intravenous tocolysis in preterm labor.

Author(s): Sayin, N Cenk; Varol, Füsun G; Balkanli-Kaplan, Petek; Sayin, Müge

Source: Journal of perinatal medicine; 2004; vol. 32 (no. 3); p. 220-224

Publication Date: 2004

Publication Type(s): Randomized Controlled Trial Clinical Trial Journal Article

PubMedID: 15188794

Abstract:AIMSOur aim was to evaluate the efficacy of maintenance oral nifedipine in pregnant women initially treated with intravenous ritodrine plus verapamil for preterm labor.METHODSThe study included 73 patients with preterm labor with intact membranes. Patients were randomized to receive either maintenance oral nifedipine therapy (n=37) administered 20 mg every six hours or no treatment (controls, n=36) after discontinuation of acute intravenous tocolysis.RESULTSCompared to the control group, the mean +/- SD time gained from initiation of maintenance therapy to delivery (26.65 +/- 18.89 vs. 16.14 +/- 12.91 days, p=0.007) and the gestational age at delivery (37.03 +/- 2.06 vs. 35.1 +/- 3 weeks, p=0.003) were higher in the nifedipine maintenance therapy group. The proportion of patients who required one or more courses of subsequent intravenous therapy and perinatal outcomes were similar in the maintenance therapy and control groups.CONCLUSIONSThe gestational age and time gained from initiation of maintenance therapy to delivery were longer in women receiving oral maintenance tocolysis with nifedipine. However, maintenance therapy did not decrease the recurrence of preterm labor episodes or improve perinatal outcomes.

Database: Medline

32. Nifedipine in pregnancy

Author(s): Smith P.; Johanson R.; Anthony J.

Source: British Journal of Obstetrics and Gynaecology; 2000; vol. 107 (no. 3); p. 299-307

Publication Date: 2000

Publication Type(s): Review

PubMedID: 10740323

Available at British Journal of Obstetrics and Gynaecology - from Wiley Online Library

Available at British Journal of Obstetrics and Gynaecology - from Unpaywall

Database: EMBASE

33. Maintenance oral nifedipine for preterm labor: a randomized clinical trial.

Author(s): Carr, D B; Clark, A L; Kernek, K; Spinnato, J A

Source: American journal of obstetrics and gynecology; Oct 1999; vol. 181 (no. 4); p. 822-827

Publication Date: Oct 1999

Publication Type(s): Randomized Controlled Trial Clinical Trial Journal Article

PubMedID: 10521736

Abstract:OBJECTIVEThis study was undertaken to evaluate the efficacy of maintenance oral nifedipine in patients initially treated with intravenous magnesium sulfate for preterm labor.STUDY DESIGNPatients with a diagnosis of preterm labor between 24 and 33.9 weeks' gestation were randomly assigned to receive either maintenance tocolytic therapy with oral nifedipine (20 mg every 4-6 hours) or no treatment (control) after discontinuation of magnesium tocolysis. Pregnancy and neonatal outcomes were evaluated. A sample size of 50 patients was required to detect a 10-day difference in mean time gained (beta =.2, alpha =.05). Statistical analyses were based on intent to treat. The t, chi(2), and Fisher exact tests were performed.RESULTSSeventy-four patients were randomly assigned to receive either oral nifedipine (n = 37) or no treatment (n = 37). There were no statistically significant differences in age, race, parity, preterm delivery risk factors, enrollment gestational age, results of cervical examination, delivery gestational age, time gained, or neonatal complications between the groups. Delivery gestational age (mean +/- SD) was 35.4 +/- 3.2 weeks for patients randomly assigned to receive nifedipine and 35.3 +/- 3.2 weeks for patients who received no treatment (P =.9). Time gained during pregnancy was 37 +/- 23.9 days in the nifedipine group and 32.8 +/- 20.4 days in the control group (P =.4).CONCLUSIONMaintenance therapy with oral nifedipine does not significantly prolong pregnancy in patients initially treated with intravenous magnesium sulfate for preterm labor.

Database: Medline

34. Nifedipine and ritodrine in the management of preterm labor: a randomized multicenter trial.

Author(s): Papatsonis, D N; Van Geijn, H P; Adèr, H J; Lange, F M; Bleker, O P; Dekker, G A

Source: Obstetrics and gynecology; Aug 1997; vol. 90 (no. 2); p. 230-234

Publication Date: Aug 1997

Publication Type(s): Randomized Controlled Trial Clinical Trial Multicenter Study Journal Article

PubMedID: 9241299

Abstract:OBJECTIVETo compare the efficacy of nifedipine with ritodrine in the management of preterm labor.METHODSOne hundred eighty-five singleton pregnancies with preterm labor were assigned randomly to either ritodrine intravenously (n = 90) or nifedipine orally (n = 95). The principal outcome assessed was delay of delivery.RESULTSRitodrine was discontinued in 12 patients because of severe maternal side effects, and their results were excluded from further analysis. More women in the ritodrine group delivered within 24 hours (22 versus 11, P = .006), within 48 hours (29 versus 21, P = .03), within 1 week (45 versus 36, P = .009), and within 2 weeks (52 versus 43, P = .005) compared with those receiving nifedipine. There were significantly fewer maternal side effects in the nifedipine group. Apgar scores and umbilical artery and vein pHs were similar in both groups. The number of admissions to the neonatal intensive care unit (NICU) in the nifedipine group was significantly lower than in the ritodrine group (68.4 versus 82.1%, P = .04).CONCLUSIONNifedipine in comparison with ritodrine in the management of preterm labor is significantly associated with a longer postponement of deliver, fewer maternal side effects, and fewer admissions to the NICU.

Database: Medline

Strategy 713269

#	Database	Search term	Results
1	Medline	exp NIFEDIPINE/	15464
2	Medline	(nifedipine).ti,ab	19232
3	Medline	(Adalat).ti,ab	174
4	Medline	((preterm OR premature OR "pre term") ADJ2 (labor OR labour)).ti,ab	10853
5	Medline	exp "OBSTETRIC LABOR, PREMATURE"/	24938
6	Medline	(4 OR 5)	29504
7	Medline	(1 OR 2 OR 3)	23150
8	Medline	(6 AND 7)	333
9	Medline	("immediate release" OR "slow release").ti,ab	10361
10	Medline	exp "DELAYED-ACTION PREPARATIONS"/	45666
11	Medline	((delayed OR controlled) ADJ2 release).ti,ab	19910
12	Medline	(9 OR 10 OR 11)	63997
13	Medline	(8 AND 12)	11
14	EMBASE	exp NIFEDIPINE/	48633
15	EMBASE	(nifedipine).ti,ab	23536
16	EMBASE	(Adalat).ti,ab	325
17	EMBASE	(14 OR 15 OR 16)	51066
18	EMBASE	((preterm OR premature OR "pre term") ADJ2 (labor OR	14736

		labour)).ti,ab	
19	EMBASE	exp "PREMATURE LABOR"/	44005
20	EMBASE	(18 OR 19)	47631
21	EMBASE	("immediate release" OR "slow release").ti,ab	14853
22	EMBASE	exp "SLOW RELEASE PREPARATION"/	1528
23	EMBASE	exp "SUSTAINED RELEASE PREPARATION"/	55728
24	EMBASE	((delayed OR controlled) ADJ2 release).ti,ab	25665
25	EMBASE	(21 OR 22 OR 23 OR 24)	91078
26	EMBASE	(17 AND 20 AND 25)	22
27	EMBASE	exp "DRUG DOSE COMPARISON"/	37507
28	EMBASE	(17 AND 20 AND 27)	6
29	EMBASE	exp "DRUG RELEASE"/	80271
30	EMBASE	(17 AND 20 AND 29)	12
31	EMBASE	exp "DOSE RESPONSE"/	399598
32	EMBASE	(17 AND 20 AND 31)	30
33	EMBASE	exp "DRUG ABSORPTION"/	81430
34	EMBASE	(17 AND 20 AND 33)	12
35	Medline	exp "GASTROINTESTINAL ABSORPTION"/	43871
36	Medline	(8 AND 35)	0
37	Medline	(7 AND 35)	89

38	Medline	(pregnan*).ti,ab	471277
39	Medline	exp PREGNANCY/	870457
40	Medline	(38 OR 39)	972694
41	Medline	(37 AND 40)	1
42	EMBASE	(pregnan*).ti,ab	605079
43	EMBASE	exp PREGNANCY/	640904
44	EMBASE	(42 OR 43)	861193
45	EMBASE	(25 AND 44)	1832
46	EMBASE	(14 AND 45)	44
47	EMBASE	exp "DRUG BIOAVAILABILITY"/	63437
48	EMBASE	(17 AND 20 AND 47)	6
49	Medline	(1 AND 5)	225
50	EMBASE	exp "DRUG DOSE COMPARISON"/	37507
51	EMBASE	(17 AND 20 AND 50)	6
52	EMBASE	*NIFEDIPINE/	19017
53	EMBASE	(19 AND 52)	329