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Diltiazem for Maintenance Tocolysis of Preterm Labor: Comparison to Nifedipine in a Randomized Trial

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Abstract The objective of this study was to compare the safety and efficacy of maintenance tocolysis with oral diltiazem to oral nifedipine in achieving 37 weeks gestation. After successful intravenous tocolysis with magnesium sulfate, 69 women with preterm labor at <35 weeks gestation were randomly assigned to nifedipine (20 mg orally every 4–6 hr), or diltiazem (30–60 mg orally every 4–6 hr). The primary outcome was the percentage of patients achieving 37 weeks gestation. Maternal cardiovascular alterations and neonatal outcomes were also assessed. Sixty-nine patients were available for final analysis. Less patients on diltiazem as compared to nifedipine achieved 37 weeks (15.1% vs. 41.7%, $P = 0.019$). Gestational age at delivery was also less for patients receiving diltiazem (35.5 ± 3.5 weeks vs. 33.4 ± 3.9 weeks, $P = 0.022$). There were fewer days gained in utero from randomization to delivery with diltiazem as compared to nifedipine; however, this difference was not statistically significant (22.4 ± 16.3 days vs. 31.2 ± 24.4 days, $P = 0.084$). Maternal blood pressure and pulse during tocolysis did not differ significantly between groups. Despite the theoretical advantages of diltiazem tocolysis, maintenance tocolysis with diltiazem offered no benefit over nifedipine in achieving 37 weeks gestation. The cardiovascular alterations with either drug in normotensive, pregnant patients appear minimal. *J. Matern.–Fetal Med. 7:217–221, 1998.*

Key words: tocolysis; diltiazem; nifedipine

INTRODUCTION

Preterm birth remains a major cause of perinatal morbidity and mortality in the United States [1]. Numerous tocolytic therapies have been introduced in an attempt to prolong gestation in pregnancies complicated by preterm labor. Significant maternal side effects from tocolysis have been described, including pulmonary edema, myocardial ischemia, cardiac arrythmias and death [2–4]. Since uterine contractility is dependent on the flux of extracellular calcium ions into myometrial smooth muscle cells, calcium channel blocking agents have been investigated for the tocolysis of preterm labor. Calcium channel-blocking agents can inhibit the flux of extracellular calcium ions through the plasma membrane voltage-sensitive channels of smooth muscle [5]. Nifedipine, a dihydropyridine calcium channel blocker, has been shown to be as effective as more established therapies for preterm labor tocolysis, but with significantly fewer maternal cardiovascular side effects [6–9]. Diltiazem, a 1,5-benzothiazepine calcium channel blocker, also has been found to inhibit uterine contractility in vitro and in vivo and has a far greater selectivity for uterine relaxation over cardiovascular effects than nifedipine [10,11]. The purpose of this study is to compare the efficacy and safety of diltiazem to nifedipine for tocolysis in humans.

SUBJECTS AND METHODS

This prospective, randomized trial was conducted at Stanford University during the period April 1992–October 1996, after approval from the university's Institutional Review Board. Women with documented preterm labor (uterine contractions and cervical change) before 35 weeks gestation and who had been successfully treated with intravenous magnesium sulfate were eligible for inclusion in this study. Exclusion criteria included ruptured membranes, the presence of a cerclage, >4 cm cervical dilation,

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placental abruption, placenta previa, a fetal anomaly not compatible with life, maternal or fetal contraindications to tocolysis, maternal history of hypertension, and maternal or fetal indications for delivery. Following informed consent, 69 patients with documented preterm labor receiving acute intravenous tocolysis with magnesium sulfate were randomly assigned to oral diltiazem or nifedipine for maintenance tocolysis. A 1:1 randomization scheme using opaque sealed envelopes was used to select treatment with either nifedipine or diltiazem. Uterine quiescence (≤4 contractions per hr and no further cervical change) was achieved with intravenous magnesium for 12–24 hours. Patients were then weaned off magnesium sulfate by 1 g per hour, maintaining ≤4 contractions per hour. The first dose of the oral agent was administered at 1 g/hr of magnesium sulfate infusion. An hour after administration of either nifedipine or diltiazem, the magnesium sulfate was discontinued. The oral dose was diltiazem 30–60 mg every 4–6 hours (maximum dose of 360 mg in 24 hr) or nifedipine 20 mg every 4–6 hours (maximum dose of 120 mg in 24 hr), and was stopped at 37 weeks. The dose of nifedipine used in this study was based on an earlier nifedipine tocolysis trial [8]. The maximum dose of diltiazem administered in this trial was based on the usual maximum oral daily dose clinically recommended [12]. Dosage of both agents was adjusted to control uterine contractions to ≤4 per hour and no further cervical change.

Persistent contractions despite maximum dose oral tocolysis were treated with a second course of intravenous magnesium sulfate. Patients successfully completing a second course of intravenous tocolysis were then placed back on the oral agent to which they were originally randomized. Maternal blood pressure and pulse were recorded prior to the start of the oral tocolytic, then every hour for 6 hours, then every 4 hours while hospitalized. The fetal heart rate was monitored continuously during the first 6 hours of oral tocolysis and then every eight hours for 30 minutes while the patient was hospitalized. Following discharge, the patients were seen weekly for a blood pressure measurement and cervical exam. A weekly nonstress test, amniotic fluid index, biophysical profile, and umbilical artery doppler velocimetry were scheduled. Patients who were unable to have the full panel of weekly antepartum testing at Stanford University were at a minimum required to have weekly nonstress testing with their referring physician, as well as a weekly cervical exam and blood pressure measurement.

The primary outcome of this study was the percentage of patients achieving 37 weeks. Other variables analyzed were days gained in utero, gestational age at delivery, birth weights and serial maternal blood pressures, and pulse rates. Neonatal outcome data included the incidence of neonatal respiratory distress syndrome and intraventricular hemorrhage. Entry characteristics and outcome variables were analyzed with two-tailed Fisher exact test or Student t-test with a Bonferroni correction for multiple comparisons as appropriate (StatView 4.5, Abacus Concepts, Berkeley, CA). Results were analyzed on an intention to treat basis.

TABLE 1. Population Characteristics Prior to Randomization[a]

	Nifedipine	Diltiazem	*P* value
n	36	33	
Gestational age (weeks)	31.1 ± 3.0	30.3 ± 2.9	NS
Cervical dilation (cm)	1.8 ± 1.1	1.9 ± 1.1	NS
Multiparity	15 (41.7%)	14 (42.4%)	NS
Multiple gestations	14 (38.9%)	12 (36.4%)	NS

[a]Data represented as mean ± SD or number and percent.
NS = not significant.

TABLE 2. Delivery Outcome by Group[a]

	Nifedipine	Diltiazem	*P* value
n	36	33	
Delivery ≥37 weeks	15 (41.7%)	5 (15.1%)	0.019
Days gained in utero	31.2 ± 24.4	22.4 ± 16.3	0.084
Re-tocolysis with magnesium sulfate	12 (33.3%)	14 (42.4%)	0.45
Gestational age at delivery (weeks)	35.5 ± 3.5	33.4 ± 3.9	0.022

[a]Data represented as mean ± SD or number and percent.

RESULTS

There were no statistically significant differences in pretreatment maternal characteristics (Table 1). Table 2 compares the delivery outcomes between the two groups. Fewer patients on diltiazem achieved 37 weeks, and the mean gestational age at delivery was less for patients in the diltiazem group. There was a nonstatistically significant fewer days gained in utero for patients on diltiazem.

Complete blood pressure and pulse values were available for 64 of the 69 patients. No significant mean arterial pressure or pulse changes were noted between treatment groups (Table 3). In addition within each group, no significant decline in systolic blood pressure, diastolic blood pressure, or change in pulse was noted between baseline and any subsequent time period.

Upon hospital discharge, antepartum testing involving a weekly nonstress test, amniotic fluid index, biophysical profile, and umbilical artery doppler velocimetry was scheduled. Twenty-three of the 36 nifedipine patients and 18 of the 33 diltiazem patients underwent one or more full antepartum testing assessments. Among the patients tested, there were no cases of a biophysical profile ≤4, absent or reversed umbilical artery doppler velocimetry, or nonreassuring nonstress test. One diltiazem patient with twins was found to have decreased amniotic fluid in both sacs at 35 weeks gestation and underwent labor induction. The 28 patients who did not get complete antepartum testing either failed tocolysis with nifedipine or diltiazem before outpa-

TABLE 3. Baseline and Interval Mean Arterial Pressure (MAP) and Heart Rate Values During Maintenance Tocolysis[a]

	Nifedipine	Diltiazem	*P* value
MAP (mm Hg)			
Baseline	74.3 ± 7.2	72.8 ± 7.1	NS
4 hours	72.7 ± 7.3	74.1 ± 7.2	NS
8–12 hours	76.4 ± 9.3	71.3 ± 8.2	NS
13–72 hours	76.8 ± 7.3	75.9 ± 5.8	NS
Heart rate			
Baseline	87.9 ± 11.3	86.3 ± 9.8	NS
4 hours	91.3 ± 11.7	87.6 ± 11.3	NS
8–12 hours	87.0 ± 13.1	83.1 ± 10.5	NS
13–72 hours	85.9 ± 10.6	83.4 ± 9.0	NS

[a]Data represented as mean ± SD.
NS = not significant.

TABLE 4. Neonatal Outcome by Group[a]

	Nifedipine	Diltiazem	*P* value
Birthweight (grams)	2337.5 ± 819	2159.9 ± 808	NS
Neonatal intensive care unit admissions (days)	9.3 ± 15.9	17.0 ± 29.9	NS
Intraventricular hemorrhage	0	1 (3.2%)	NS
Respiratory distress syndrome	4 (12.5%)	4 (13.0%)	NS
Five minute Apgar score <7	0	3	NS

Data represented as mean ± SD.
NS = not significant.

tient testing could be initiated (n = 18), or were transferred back to their referring physicians where the full panel of tests were not performed (n = 4), or failed to follow up for scheduled antepartum testing (n = 6). Among the patients who delivered prior to hospital discharge and weekly antepartum testing, there were no cases of induced delivery for an abnormal fetal heart rate.

Gestational age at delivery was obtained for all the patients in this study. However, additional neonatal data regarding possible respiratory distress syndrome, intraventricular hemorrhage, and days in the neonatal intensive care unit could not reliably be obtained for six patients due to incomplete neonatal medical records (3 nifedipine patients and 3 diltiazem patients). Of the newborns whose records were available, there was no difference in the incidence of neonatal respiratory distress syndrome or intraventricular hemorrhage between the two treatment groups. Although babies whose mothers received nifedipine weighed on average 178 g more and spent a mean of 8 fewer days in the neonatal intensive care nursery than babies whose mothers received diltiazem, these differences were not statistically significant (Table 4).

DISCUSSION

The uterine relaxant properties of nifedipine and diltiazem have been documented in vivo and in vitro [10,13–17]. Diltiazem tocolysis was further investigated by Holbrook et al. [18] using an intravenous bolus dose of oxytocin to induce parturition in the near-term pregnant rabbit. Parturition was markedly inhibited in the rabbits that received diltiazem as compared to those receiving saline.

The minimal maternal cardiovascular side effect profile associated with nifedipine tocolysis in humans is also well documented [6,9]. Nonetheless, animal data are conflicting regarding the degree of maternal and fetal hemodynamic alteration associated with nifedipine tocolysis [19–21]. Sublingual nifedipine followed by oral nifedipine during tocolysis has been shown to cause a transient decline in diastolic and mean arterial pressures and a transient rise in heart rate in pregnant, normotensive women [9]. Diltiazem has been called the most balanced calcium antagonist in regard to cardiovascular side effects [11]. Unlike nifedipine, diltiazem has very little negative inotropic effect. Furthermore, secondary to its slowing effect on A-V node conduction, diltiazem is not associated with the reflex tachycardia occasionally described with nifedipine [22]. Granger et al. [10] investigated the potency and selectivity of nifedipine and diltiazem as inhibitors of tension development by the uterus and cardiovascular tissues from the term pregnant rat. Both nifedipine and diltiazem inhibited tension development by the uterus. However, diltiazem had a far greater selectivity for uterine relaxation over cardiovascular effects as compared to nifedipine.

Given diltiazem's greater uterine selectivity, we attempted to compare the tocolytic efficacy and cardiovascular profile of diltiazem to nifedipine clinically. To our knowledge this is the first clinical trial of diltiazem tocolysis. Assuming a 70% incidence of preterm delivery for maintenance tocolysis [23], we calculated that a total of at least 60 patients would be required to detect a 50% reduction in the incidence of preterm delivery with the use of diltiazem, with alpha = 0.05 and a power of 80%.

Patients offered enrollment in this study were those patients in preterm labor who met the study's inclusion criteria. We attempted to offer all patients meeting these criteria enrollment and randomization. Eligible patients not enrolled in this study were predominantly those who refused experimental drug therapy, or whose private physicians voiced a preference for standard maintenance tocolytic therapy with nifedipine or terbutaline.

In this prospective, randomized trial diltiazem offered no benefit over nifedipine for the maintenance tocolysis of preterm labor. In fact fewer patients receiving diltiazem as compared to nifedipine reached 37 weeks gestation, which was the primary outcome parameter of this study. There were no statistically significant differences between treatment arms regarding cervical dilation and gestational age at

the initiation of oral tocolysis. The dosing for nifedipine was based on doses used in a previous nifedipine tocolysis trial [8], as well as standard nifedipine dosing at our institution. No adequate data existed prior to this study for diltiazem tocolytic dose and dose intervals. Although it is possible that the theoretical benefit of greater uterine selectivity with diltiazem may have been manifested at higher doses, in designing this clinical trial we allowed for use of the usual maximum dose of oral diltiazem clinically recommended [12]. Given the limited clinical experience in pregnancy with diltiazem, the dose range was of necessity broader than with nifedipine to allow for appropriate individualization and adjustment of diltiazem tocolytic therapy. The dose and dosage intervals for both nifedipine and diltiazem were initially determined by the clinical stability of the patient, and doses were increased to the maximum allowable as needed to control breakthrough contractions or recurrent preterm labor.

Although it has been our practice to offer maintenance tocolysis to all our patients with arrested preterm labor, debate continues in the literature regarding the effectiveness of maintenance tocolysis. Some authors report no benefit in pregnancy prolongation or reduction in recurrent premature labor with oral maintenance therapy as compared with placebo [23–25]. Other investigators have suggested a significant advantage with maintenance therapy [26–28]. In general these trials have studied maintenance therapy with betamimetics or oral magnesium chloride versus placebo. Whether calcium channel blockers, which are known not to induce tachyphylaxis, are more effective than betamimetics or placebo for the purpose of maintenance tocolysis is an issue that will need to be addressed in further trials. However, a recent study by Papatsonis et al. [29], in which nifedipine was compared to ritodrine for both acute and maintenance tocolysis, demonstrated a significantly longer postponement of delivery in patients receiving nifedipine as compared to those receiving ritodrine.

We found no difference in mean arterial pressure or pulse changes between nifedipine and diltiazem and no significant decline in blood pressure or change in pulse from baseline with either drug in this group of normotensive, pregnant women. Read and Wellby [6] also failed to show any significant changes in maternal heart rate or blood pressure during nifedipine tocolysis. However, Ferguson et al. [9], using sublingual nifedipine followed by oral nifedipine, showed a transient decline in diastolic and mean arterial pressure and a transient rise in pulse during the first 6 hours of nifedipine administration. Sublingual nifedipine was not used in our study, which may explain the differences between our results and those of Ferguson et al. [9]. Furthermore, the timing of our measurements differs from that of Ferguson et al. [9] and was designed to detect persistent cardiovascular alterations up to the first 72 hours of tocolysis.

Although human data with calcium channel blocker tocolysis is reassuring in regard to maternal and fetal cardiovascular effects, given that some animal studies have reported adverse fetal hemodynamic changes with these agents, we attempted to evaluate the safety of nifedipine and diltiazem tocolysis using available antepartum testing modalities (nonstress test, amniotic fluid index, biophysical profile, and umbilical artery doppler study). The results of our study lend support to the overall safety of calcium channel blocker tocolysis in humans.

We conclude that despite the theoretical advantages of diltiazem tocolysis, diltiazem offers no benefit over nifedipine in achieving 37 weeks gestation. In fact, fewer patients on diltiazem reached term. The cardiovascular side effects associated with either diltiazem or nifedipine tocolysis in the normotensive, pregnant patient appear to be minimal.

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