MAINTENANCE TOCOLYTIC THERAPY WITH ORAL TERBUTALINE OR SUBCUTANEOUS TERBUTALINE INFUSION BY PUMP FOR PREVENTION OF PRETERM DELIVERY

ISSUE

Blue Shield continues to receive requests for coverage of maintenance tocolytic therapy with oral terbutaline or subcutaneous terbutaline infusion by pump for prevention of preterm delivery.

CURRENT BLUE SHIELD POLICY

The current Blue Shield of California policy on tocolytic therapy using terbutaline dates from September 13, 1989. The policy states that, “Terbutaline tocolytic therapy is eligible for coverage when administered intravenously, subcutaneously or orally. Subcutaneous terbutaline pump tocolytic therapy is investigational and not eligible for coverage.”

The topic was reviewed again by the Medical Policy Committee on Quality and Technology (MPCQT) in 1992, but the Committee made no change in policy. However, since then, a series of articles, including 7 randomized trials, have been published concerning maintenance tocolytic therapy with oral terbutaline or subcutaneous terbutaline infusion. Therefore, the Medical Policy Committee on Quality and Technology is asked to re-review the published data regarding the efficacy and safety of terbutaline for maintenance tocolytic therapy in clinical practice.

BACKGROUND

Preterm birth is associated with significant neonatal mortality and morbidity nationwide. Preterm labor is variously defined as increased frequency of uterine contractions; documented changes in the cervix, such as dilatation or effacement; premature rupture of the membranes; and gestational age under 37 weeks. The national rate of prematurity from preterm birth approaches 11%. Despite widespread use of tocolytic agents, the preterm birth rate has actually increased over the past 30 years in the U.S. (Mauldin et al., 2001). The main treatments aimed at prolonging pregnancy in those experiencing and preterm labor are bed rest and medications to inhibit uterine contractions (tocolytic agents). Bed rest (usually at home) is widely recommended, though there are no studies of its efficacy in reducing adverse neonatal outcomes.
Short-Term Tocolytic Therapy with Parenteral Agents

A variety of parenteral tocolytic agents to reduce uterine contractions have documented efficacy in delaying delivery for 24 to 48 hours (U.S. Preventive Services Task Force, 1993). Effective agents include magnesium sulfate (Spisso et al., 1982; Elliot, 1983; Hollander et al., 1987), beta-agonists such as ritodrine and terbutaline (Ingemarsson, 1976; Beall et al., 1985; King et al., 1988; Hollander et al., 1987; Wenstrom et al., 1997); and non-steroidal anti-inflammatory agents such as indomethacin (Morales et al., 1993). This 24-48 hour prolongation of pregnancy can be beneficial by allowing transfer of mother and fetus to a tertiary care center and by providing time for antenatal corticosteroid administration (Wenstrom et al., 1997). Corticosteroids can reduce mortality, respiratory distress syndrome, and intraventricular hemorrhage in preterm infants between 24 and 34 weeks gestation (NIH, 1994).

About two-thirds of all patients with preterm labor are not candidates for continued tocolytic therapy beyond the initial 48-hour period. Many progress in labor and deliver. Others developed fetal or maternal complications which contraindicate continued tocolytic therapy (Wenstrom et al., 1997).

Maintenance Tocolytic Therapy with Oral Terbutaline

In the remaining one-third of patients, after the arrest of preterm labor with parenteral tocolytics, oral tocolytic agents are often prescribed as maintenance therapy in an attempt to reduce the rate of recurrent preterm labor (Rust et al., 1996). Oral agents that have been administered include the beta-agonists such as the asthma medication, terbutaline.

However, its clinical efficacy has remained quite controversial. Studies have suggested several potential problems with use of oral beta-agonist agents like terbutaline for maintenance tocolytic therapy. First, oral administration of beta-agonists results in variable drug levels, with peaks and troughs. Second, the requirement for every 4-6 hour dosing results in problems with compliance. Third, long-term exposure to beta-agonist agents results in desensitization of the beta-adrenergic receptors in the myometrium and development of tolerance to its effects. To overcome these problems, subcutaneous administration of terbutaline was first developed (Stubblefield, 1982), and later a portable pump was developed for its continuous subcutaneous administration as maintenance therapy (Lam et al., 1988; Gill et al., 1989; Fischer et al., 1992).
Maintenance Tocolytic Therapy with Subcutaneous Terbutaline Infusion by Pump

The portable terbutaline pump is similar in design to the insulin pump. It enables subcutaneous administration of terbutaline via an automated, programmable infusion pump. The pump provides a constant low maintenance rate of drug delivery and permits preprogrammed additional boluses of the tocolytic agent to be administered at times when uterine contractions develop. It has therefore been proposed as an optimal method for administration of outpatient beta-agonist maintenance tocolytic therapy.

TA Criterion 1: The technology must have final approval from the appropriate government regulatory bodies.

The approved FDA labeling for terbutaline sulfate (Bethine® tablets and injection) states, “Terbutaline sulfate is indicated for the prevention and reversal of bronchospasm in patients 12 years of age and older with asthma and reversible bronchospasm associated with bronchitis and emphysema…Terbutaline sulfate has not been approved and should not be used for tocolysis” (PDR, 2002).

Infusion pumps are not specifically labeled for subcutaneous administration of terbutaline. The FDA issued a letter to physicians on November 13, 1997 concerning the use of terbutaline sulfate by subcutaneous injection (see Patient Risks below). Regarding terbutaline, the letter states, in part, “the drug should not be used for the management of preterm labor.”

TA criterion 1 is not met.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

The published literature concerning maintenance tocolytic therapy with oral terbutaline consists of various case series, 1 nonrandomized comparative trial, 5 randomized controlled trials, 1 meta-analysis, and 1 systematic review.

The published literature concerning maintenance tocolytic therapy with subcutaneous terbutaline infusion by pump consists of various case series, 1 nonrandomized comparative trial, and 2 randomized controlled trials.
TA Criterion 2, continued

Outcomes assessed in the various clinical trials have varied, but have most often included the following measures: incidence of preterm delivery, incidence of recurrent preterm labor, latency from treatment to delivery (prolongation of pregnancy), gestational age, mean birth weight, admission to a neonatal intensive care unit (ICU), incidence of infant respiratory distress syndrome, incidence of intraventricular hemorrhage, and perinatal mortality.

TA criterion 2 is met.

Levels of Evidence: 1, 4, 5

TA Criterion 3: The technology must improve the net health outcomes.

Efficacy

A. Efficacy of Oral Terbutaline Maintenance Therapy

1. Nonrandomized Comparative Trial

In a prospective nonrandomized trial, Brown and colleagues (1997) evaluated the impact of intravenous and oral tocolysis on prolongation of gestation in 200 women with preterm uterine contractions without cervical changes (group 1) and 175 women with actual preterm labor (group 2), that is, uterine contractions plus cervical changes at presentation or developing under observation. Following intravenous magnesium sulfate tocolysis, both groups received oral terbutaline maintenance therapy until 37 weeks’ gestation. Primary outcome variables included the length of gestation obtained following initial treatment and the preterm birth rate. Results showed that, as might be expected, women in group 2 were twice as likely to deliver before 35 weeks (23% vs. 9.5%, respectively, p < 0.05), and to deliver before 37 weeks (45% versus 22%, p < 0.05). However, there was no significant difference in days gained in utero for women on oral terbutaline for either group. There was also no significant difference in gestational age at delivery between the two groups. Oral terbutaline tocolytic therapy had no significant effect on birth weight, infant days in hospital, days in the neonatal ICU, and days requiring ventilatory assistance in either group. The authors concluded that maintenance tocolysis with oral terbutaline had no significant impact on further prolongation of pregnancy after intravenous tocolysis. This trial was nonrandomized and the authors acknowledge the possibility of a selection bias.
TA Criterion 3, continued

2. Randomized, Controlled Trials

The best available evidence derives from the 6 prospective, randomized, controlled trials of oral terbutaline sulfate as maintenance tocolytic therapy; 5 of the 6 showed no effect.

The one randomized, controlled trial suggesting benefit from oral terbutaline sulfate as maintenance tocolytic therapy was an early one by Brown et al. (1981). These authors reported a randomized comparison of oral terbutaline to placebo. In this study, 46 patients in premature labor were initially successfully treated with ethanol infusion; 23 were then given prolonged oral terbutaline until 38 weeks' gestation, and the other 23 were given placebo. Results showed that the terbutaline group gained significantly more time in gestation than the placebo group (p < .05). In addition, idiopathic respiratory distress syndrome occurred significantly less often in the terbutaline-treated group. There was no perinatal mortality in either group. However, in this study, only regular uterine contractions and not a change in cervical examination were required for the diagnosis of premature labor, and thus some of the patients may not have been in true preterm labor. In addition, the two groups differed significantly in baseline Bishop score (an assessment of cervical dilatation and effacement by digital examination), and in the number of twin pregnancies, suggesting possible inadequate randomization. Finally, the dose of terbutaline was standardized and not adjusted based upon the patient’s response to it.

The remaining 5 randomized, controlled trials found no benefit from oral terbutaline sulfate as maintenance tocolytic therapy.

Howard et al. (1982) conducted a prospective, randomized, double-blind and study of 33 women with premature labor. Patients were randomized to receive either terbutaline by the intravenous route, and then, if successful, by the subcutaneous then oral routes (n=15) versus placebo (dextrose) (n=18). Mean maternal age, gestational age, cervical dilatation, and uterine activity were similar in both groups on admission. Results showed no statistically significant differences in pregnancy outcomes: prolongation of gestation (terbutaline, 30.8 days versus placebo, 39.9 days, p=N.S); mean birth weight (terbutaline, 2487 g vs. placebo, 2756 g, p=N.S.); and incidence of neonatal respiratory distress syndrome (p=N.S.).
TA Criterion 3 (2. Randomized, Controlled Trials), continued

Parilla et al. (1993) prospectively randomized 55 patients to either oral terbutaline (n = 28), or no therapy (n = 27) after successful intravenous intravenous magnesium sulfate tocolysis. The dose of terbutaline was individualized to achieve a maternal pulse > 100 beats/min, and the drug was continued until completion of 36 weeks gestation. Recurrent preterm labor (contractions with change in cervical examination) for either group was treated with intravenous magnesium sulfate, and subsequent treatment was based on the previous randomization. Results showed no difference between groups with respect to time gained (4.0 ± 2.7 vs. 4.6 ± 3.1 weeks, p = 0.412); gestational age at delivery (35.6 ± 2.7 vs. 36.1 ± 2.4 weeks, p = 0.562); delivery at ≥ 37 weeks (9 vs. 13, p = 0.291); recurrent preterm labor (10 vs. 4, p = 0.104); recurrent uterine contractions alone (5 vs. 8, p = 0.527); birth weight (2616 ± 633 gm vs. 2645 ± 599 gm, p = 0.785); intensive care nursery admissions (8 vs. 6, p = 0.759); or neonatal respiratory distress syndrome (3 vs. 2, p = 0.965). The authors concluded that use of oral terbutaline after successful parenteral tocolysis failed to reduce the rate of preterm birth. This trial was not placebo-controlled, and thus was not double-blinded.

In a larger study, after initial successful intravenous magnesium tocolysis, How et al. (1995) prospectively randomized 184 patients with preterm labor to continued bed rest either with or without oral terbutaline. Assignment was made with stratification into four groups: group 1 were patients with a Bishop score ≥ 5 given oral terbutaline (n = 50); group 2, were those with a Bishop score ≥ 5 given no oral medication (n = 53); group 3, those with a Bishop score < 5 given oral terbutaline (n = 41); group 4, those with a Bishop score < 5 given no oral medication (n = 40). Results showed no statistically significant differences were found in the number of readmissions or the number of unscheduled hospital visits. There were also no differences in neonatal outcomes (morbidity, mean length of nursery stay, birth weight, ventilatory support, oxygen requirement) among the four groups. The gestational age at delivery and percent of deliveries at ≥37 weeks were not significantly different when group 1 was compared with group 2 and group 3 was compared with group 4. A comparison of all patients randomized to the oral terbutaline arm (groups 1 and 3) and the no oral terbutaline arm (groups 2 and 4) also revealed no significant differences in pregnancy and neonatal outcomes. The authors concluded that oral terbutaline maintenance therapy does not improve pregnancy outcome in patients who have had initial successful intravenous tocolysis. Again, this trial was not placebo-controlled, and thus was not double-blinded.
Lewis and colleagues (1996) sponsored another large randomized, double-blind, placebo-controlled trial of oral terbutaline maintenance. After successful intravenous magnesium sulfate tocolysis, 203 women with preterm labor were randomized to oral terbutaline or placebo until 37 weeks' gestation. Pregnancy outcome data were available in 200 women. The authors found no significant differences between the terbutaline and placebo groups in the percentage of infants delivered within 1 week of starting oral tocolytic therapy (18% vs. 24%, respectively, p = N.S.); mean gestational age at delivery (35.6 vs. 36.2 weeks, p = N.S.); in the incidence of recurrent preterm labor (20% vs. 16%, p = N.S.); or in median latency (prolongation of pregnancy) (p = N.S.). Post hoc (after the results were obtained) evaluation of 96 women enrolled before 32 weeks' gestation did suggest pregnancy prolongation with maintenance oral terbutaline (p < .01); however, such post hoc data analysis is considered unreliable (Legace, 1997). The authors properly concluded that maintenance oral terbutaline therapy was not associated with pregnancy prolongation or a reduction in the incidence of recurrent preterm labor. As in previous studies, recurrent preterm labor in patients of either group was treated with intravenous magnesium sulfate, and subsequent treatment was based on the previous randomization. However, unlike prior studies, after a second recurrence, patients were restarted on the physician’s choice of medication and removed from the study. This could have resulted in bias as a result of more women on placebo having recurrent labor and thus being dropped from the study (Legace, 1997). However, the incidence of ≥1 episode of recurrent preterm labor was similar in terbutaline (20%) and placebo (16%) groups, and the study’s data were analyzed on the basis of intent to treat.

In the largest double-blind, placebo-controlled randomized trial published to date, Rust et al., 1996) reported results among three groups of women with preterm labor stabilized with acute tocolytic therapy: those given placebo (n = 68), oral terbutaline (n = 72), or oral magnesium chloride (n = 65). All subjects were enrolled in a comprehensive system of preterm birth prevention that included preterm labor education, weekly clinic visits, home uterine contraction self-assessment, daily phone contact, and 24-hour perinatal nurse access. Results showed that, when confounding variables such as the number of twin gestations were controlled for, all 3 groups had similar perinatal outcomes. The terbutaline group had significantly more side effects than the placebo group. The authors concluded that maintenance oral tocolytic therapy did not decrease uterine activity, reduce the rate of recurrent preterm labor or preterm birth, or improve perinatal outcome.
TA Criterion 3 (2. Randomized, Controlled Trials), continued

Thus, only 1 of the 5 prospective randomized trials examining the efficacy of oral terbutaline after successful intravenous tocolysis has demonstrated a reduction in the rate of preterm delivery, and this trial had several methodological flaws.

3. Meta-Analysis

One meta-analysis (Macones et al., 1995) pooled and examined the data from four randomized trials of oral beta-agonists as maintenance therapy. Trials included in this meta-analysis underwent trial quality evaluation and data abstraction independently by two blinded investigators. An estimate of the odds ratio (OR) and risk difference was calculated for the dichotomous outcomes using both a random effects model and a fixed effects model. Continuous outcomes were pooled using a simple weighted average of the within-study difference in means. The pooled OR for preventing preterm delivery was 1.09 (95% confidence interval [CI] 0.60-1.99) and the OR for preventing recurrent preterm labor was 1.05 (95% CI 0.53-2.05). The pooled difference in the mean interval to delivery was -0.22 days (95% CI -2.5 to +1.99). The authors concluded that the available data do not support the efficacy of beta-agonist maintenance therapy after resolution of an acute episode of preterm labor in reducing the incidence of preterm delivery, in increasing latency (prolongation of pregnancy), or in reducing the incidence of recurrent preterm labor.

4. Systematic Review

Meirowitz and colleagues (1999) reasoned that a formal meta-analysis of the 7 prospective randomized trials evaluating the efficacy of oral tocolytic maintenance therapy was not possible. In their view, the published trials had little in common with respect to treatment comparisons and had inconsistent definitions of outcome variables, making the pooling of data inappropriate and invalid. Instead, they performed a systematic review of these 7 trials evaluating the efficacy of maintenance therapy with oral tocolytics. Studies were included which: 1) randomized patients to an oral tocolytic after stabilization with parenteral therapy; 2) reported results for either a placebo or a control group; and 3) included patients with intact membranes only. The authors found 7 studies which met the inclusion criteria, 4 of which used oral terbutaline for the treatment arm (2 had a control group, and 2 had a placebo group), and 1 used oral ritodrine (with a placebo group).
TA Criterion 3 (4. Systematic Review), continued

Of the remaining 2 studies, one used oral terbutaline and oral magnesium chloride (with a placebo group), and the other used oral ritodrine and oral magnesium chloride (with a control group). The results of the individual studies suggest that there was no beneficial effect of oral tocolytic therapy on the incidence of preterm delivery (odds ratio (OR) range: 0.7-2.0), incidence of preterm labor recurrence (OR range: 0.6-3.2), neonatal ICU admissions (OR range: 1.3-2.0), incidence of RDS (OR range 0.1-4.3), incidence of intraventricular hemorrhage (OR range 0.3-2.0), perinatal mortality (OR range: 1.6-4.3), or gestational age at delivery.

B. Efficacy of Subcutaneous Terbutaline Infusion Pump Maintenance Therapy

1. Case Series

Several case series of subcutaneous terbutaline infusion pump tocolytic therapy have been published.

Lam et al. (1988) administered subcutaneous terbutaline via a portable infusion pump in 9 patients with preterm labor. The authors reported that the mean gestational age at initiation of therapy was 29.6 ± 3.7 weeks, and pregnancy was prolonged an average of 9.2 ± 4.3 weeks since the minimum gestational age at delivery was 37.3 weeks. Patients tolerated the therapy well; in a total 394 patient-days of therapy, there were no significant complications.

Sala et al. (1990) found the terbutaline pump efficacious in 9 of 13 patients with preterm labor who had failed other tocolytic therapies.

Moise and colleagues (1992) evaluated its usefulness in 10 singleton gestations, 1 twin pregnancy, and 2 triplet pregnancies in which other tocolytic regimens had failed. In 3 cases, the terbutaline pump was considered successful (duration of pump therapy, 52.7 ± 20.9 days; gestational age at delivery, 37.1 ± 1.3 weeks); in 6 cases, and marginally successful (duration, 42.2 ± 27.7 days; gestational age at delivery, 33.8 ± 2.6 weeks). In 4 patients, the pump had to be discontinued after 2 to 23 days because of maternal complications. The authors felt that they achieved only limited success in the small number of patients studied.
B. Efficacy of Subcutaneous Terbutaline Infusion Pump Maintenance Therapy (1. Case Series), continued

In a study of 51 patients, Adkins et al. (1993) reported that home terbutaline pump therapy was successful in 98% of the cases, prolonging pregnancy an average of 6.6 weeks. Mean gestational age at delivery was 37 ± 1.4 weeks, and infant birth weight averaged 3 kg. Overall, 22% of infants required admission to the neonatal intensive care unit, with a mean length of stay of 7.3 days.

Elliott et al. (1998) performed a retrospective review of terbutaline pump tocolytic therapy in patients with triplet (n = 15) and quadruplet (n = 6) pregnancies. The 15 patients with triplets delivered at a mean gestational age of 33 ± 1.9 weeks, and the 6 patients with quadruplets at 33 ± 1.3 weeks. Only 2 of 15 (13%) of the triplets and 1 of 6 (17%) of the quadruplets were delivered for tocolytic failure.

The largest case series was that reported by Allbert and colleagues (1992), retrospective analysis of data from 992 patients at high risk for preterm delivery who were prescribed therapy. These investigators found that the subcutaneous terbutaline therapy extended the gestation a mean of 38 ± 23 days; the average gestational age at delivery was 36.3 ± 2.6 weeks and the mean birth weight was 2759 ± 681 g. The authors concluded that prospective, randomized studies evaluating this treatment were indicated.

It must be noted that most of these case series enrolled only small numbers of patients, that they had mixed results, and that they employed no control groups to allow comparison of their results to those achievable with standard obstetric management.

2. Nonrandomized, Comparative Trial

One comparative trial of subcutaneous terbutaline infusion pump tocolytic therapy has been published.

Allbert et al. (1994) performed a retrospective analysis of a controlled study of 32 patients with recurrent preterm labor, comparing terbutaline by pump with oral terbutaline. Patients in two groups were matched for age, race, parity, gestational age and cervical dilation at diagnosis of recurrent preterm labor. Results showed that patients using the pump were more likely to reach term and less likely to fail tocolytic therapy than were those taking oral terbutaline. However, this trial was small and nonrandomized.
B. Efficacy of Subcutaneous Terbutaline Infusion Pump Maintenance Therapy (2. Nonrandomized, Comparative Trial), continued

There have been a variety of explanations for the mixed results of the case series and nonrandomized, comparative trial. For example, the dosing of the subcutaneous terbutaline infusion therapy may be critical (Lam, 1992). Others report that good compliance and high educational attainment of some patients may have contributed to the positive outcomes they achieved with this therapy (Adkins et al., 1993).

3. Randomized Controlled Trials

The best available evidence derives from the 2 prospective, randomized, placebo-controlled trials of the efficacy of subcutaneous terbutaline infusion pump tocolytic therapy.

In the trial of Wenstrom et al. (1997), patients in preterm labor (as defined by progressive cervical change) were first hospitalized and given tocolytic therapy by intravenous magnesium sulfate (with or without oral indomethacin, as needed). Once labor was arrested, patients were randomized to one of three treatments: terbutaline by pump (blinded) (n = 15), saline by pump (blinded) (n = 12), or oral terbutaline (n = 15). If recurrent preterm labor occurred despite maximization of therapy, the treatment being given was determined and then switched; saline pump and oral terbutaline were switched to terbutaline pump, terbutaline pump was switched to oral terbutaline. Patients who continued in labor were readmitted for aggressive intravenous therapy. Women in the three groups were similar in number of prior pregnancies and deliveries, days of tocolysis before study entry, gestational age at entry, and cervical dilatation at entry. Results showed that the mean gestational age at delivery was the same in all three groups (35.7 weeks in the terbutaline pump group versus 35.4 in the saline pump group versus 34.3 in the oral terbutaline group). There were also no significant differences in neonatal outcomes, including mean birth weight, median Apgar scores, complications, and mean number of days in hospital. These results indicated that terbutaline by pump and oral terbutaline were no better than saline placebo the prevention of preterm delivery. The authors concluded that terbutaline pump tocolytic therapy remained experimental.
B. Efficacy of Subcutaneous Terbutaline Infusion Pump Maintenance Therapy (3. Randomized Controlled Trials), continued

Guinn and colleagues (1998) performed a double-blind trial of terbutaline pump maintenance therapy for prevention of preterm delivery. The study enrolled women with a singleton gestation and intact membranes who had uterine contractions and >1 cm cervical dilation, 80% effacement, or progressive cervical change and whose contractions had been successfully arrested with intravenous magnesium sulfate. The authors randomly assigned the women to receive either terbutaline or placebo (normal saline) by the subcutaneous infusion pump according to a standardized protocol. Pump therapy was discontinued and parenteral magnesium was resumed if recurrent preterm labor developed. If recurrent labor was arrested, pump therapy was restarted according to the original treatment assignment. Analyses were conducted to on an intent-to-treat basis. Overall, 24 women received terbutaline and 28, placebo. Women in the two groups were similar with respect to age, race, parity, previous preterm delivery, gestational age, and cervical examination. Results showed that there was no significant difference in mean time to delivery between the groups (terbutaline 29 ± 22 days vs. placebo 28 ± 23 days, p = .78), or in mean gestational age at delivery (terbutaline 34.4 ± 3.41 weeks vs. placebo 34.9 ± 4.1 weeks, p = .56). There were no significant differences in the rates of preterm delivery at <34 weeks’ gestation (10% vs. 12%, respectively, p=.93) and <37 weeks' gestation (17% vs. 17%, respectively, p=.44). Neonatal outcomes were similar, including mean birth weight (terbutaline 2349 ± 770 g vs. placebo 2324 ± 768 g, p=.95), neonatal ICU admissions (43.5% vs. 46.4%, respectively, p=.28) or respiratory distress syndrome (8.7% vs. 14.8%, respectively, p=.51). There were also no significant differences in outcomes between women who continued and those who discontinued terbutaline therapy. The authors concluded that maintenance terbutaline therapy administered by pump did not prolong gestation in women successfully treated for suspected preterm labor.

Thus, both randomized controlled trials suggest that subcutaneous terbutaline infusion pump tocolytic therapy is no more effective than oral terbutaline or saline placebo.
C. Efficacy of Oral Terbutaline vs. Subcutaneous Terbutaline Infusion Pump Maintenance Therapy

Nonrandomized Comparative Trials

In a retrospective, matched-cohort study, Lam et al. (2001) compared the clinical effectiveness of treating recurrent preterm labor with continuous subcutaneous terbutaline versus oral tocolytics in twin gestations. Twin pregnancies treated as outpatients with continuous subcutaneous terbutaline were identified from a perinatal database, then matched 1:1 by gestational age at recurrent preterm labor to those receiving oral tocolytics (terbutaline, nifedipine, indomethacin, oral magnesium, or combination thereof). There were 353 patients per treatment group. Results showed that infants of the subcutaneous terbutaline group had greater gestational age at delivery, higher birth weights, and less frequent neonatal intensive care unit admission. The authors concluded that improved clinical outcomes and decreased nursery utilization suggested continuous subcutaneous terbutaline had greater effectiveness than oral tocolytics for the treatment of recurrent preterm labor. However, this trial had an unusual design in that it matched patients developing recurrence of preterm labor whose physicians prescribed subcutaneous terbutaline with others whose physicians prescribed a variety of oral agents. Why physicians selected one or the other treatment cannot be determined, and the regimens were not standardized.

In another retrospective study, Elliott et al (2001) assessed pregnancy prolongation in triplet pregnancies identified from a database of patients who received perinatal home care services. Patients (n = 104) were treated first with oral terbutaline following an episode of “threatened” preterm labor, then were treated with continuous subcutaneous terbutaline infusion after recurrence of preterm contractions. The primary outcome studied was gestational gain with oral terbutaline vs. subcutaneous terbutaline infusion. Results indicated that significantly greater gestational gain was achieved during subcutaneous tocolytic treatment than during oral treatment (mean 5.4 ± 3.4 vs. 2.8 ± 2.2 weeks, p < .001). The authors concluded that gestational gain was greater in triplet pregnancies during treatment with continuous subcutaneous terbutaline infusion than with oral terbutaline. However, it appears that many of the women in this trial with “threatened” preterm labor simply had uterine contractions without cervical changes, i.e., did not have actual preterm labor. The authors state that the diagnosis of threatened preterm labor and decision to prescribe and/or change tocolytic route was made by each patient physician. In addition, women were treated sequentially and thus were apparently at different gestational age when given the oral and subcutaneous terbutaline.
C. Efficacy of Oral Terbutaline vs. Subcutaneous Terbutaline Infusion Pump Maintenance Therapy (Nonrandomized Comparative Trials), continued

In both of these trials, type and specific dose of parenteral tocolysis and the findings on cervical examinations during hospitalization were not documented. The dosage of terbutaline given orally or subcutaneous was individualized as determined by the patient’s physician and not by the study protocol. Other aspects of patient management including antenatal testing, recommended activity level, hospitalization, and timing of delivery was also at the discretion in each patient’s attending physician. Finally, both trials did not feature a placebo or untreated group to determine if either form of treatment was more effective than the placebo or no medication. Finally, as acknowledged by the authors, the retrospective, non-randomized design of the analyses limit what may be concluded from these studies (Lam et al., 2001).

Patient Risks

Contraindications to terbutaline therapy include heart disease, insulin-dependent diabetes mellitus, and intolerance of the drug. Two review of the risks and complications of tocolysis, including both maternal and fetal and neonatal side effects of oral terbutaline and subcutaneous terbutaline infusion pump maintenance therapy, have been published (Hill, 1995; Lam, 1998).

The PDR states, “Serious adverse reactions may occur after administration of terbutaline sulfate to women in labor. In the mother, these include increased heart rate, transient hyperglycemia, hypokalemia, cardiac arrhythmias, pulmonary edema, and myocardial ischemia. Increased fetal heart rate and neonatal hypoglycemia may occur as a result of maternal administration.” (PDR, 2002)

A. Risks of Oral Terbutaline Maintenance Therapy

Both morbidity and mortality have been reported after maintenance oral terbutaline therapy for the suppression of preterm labor. Side effects of nervousness, palpitations and tremors are common (How et al., 1995; Rust et al., 1996). Case reports of serious toxicity include maternal myocardial infarction and coronary artery dissection in a patient who received subcutaneous terbutaline followed by oral maintenance therapy (Athanassiou et al., 1996), and maternal cardiovascular collapse (Carpenter et al., 1984).
A. Risks of Oral Terbutaline Maintenance Therapy, continued

Several prospective clinical studies have documented that maintenance oral terbutaline tocolytic therapy is associated with maternal glucose intolerance (Main et al., 1987; Angel et al., 1988; Peterson et al., 1993). This glucose intolerance may be related to decreased peripheral insulin sensitivity and increased endogenous glucose production (Smigaj et al., 1998). One study documented neonatal hypoglycemia in several infants born to mothers who received parenteral followed by oral maintenance beta-mimetic (terbutaline or fenoterol) therapy (Epstein et al., 1979); affected infants had higher cord serum insulin concentrations, perhaps related to drug-induced increases in maternal glucose concentrations.

B. Risks of Subcutaneous Terbutaline Infusion Pump Maintenance Therapy

Both morbidity and mortality have been reported after long-term subcutaneous terbutaline infusion for the suppression of preterm labor. Case reports include maternal hepatitis (Quinn et al., 1994); maternal sudden death (Hudgens et al., 1993); maternal diabetic ketoacidosis and transient severe insulin resistance (Tibaldi et al., 1990); neonatal cardiovascular toxicity (Thorkelsson et al., 1991); and neonatal myocardial necrosis (Fletcher et al., 1991). Others have noted that patients given subcutaneous or intravenous terbutaline infusion for tocolytic therapy have developed shortness of breath and tremors, leading to its discontinuation (Carpenter et al., 1984). Katz et al (1981) documented severe cardiovascular complications (pulmonary edema, myocardial ischemia) in 8 (5%) of 160 patients treated with intravenous, then subcutaneous terbutaline for preterm labor.

In contrast, Perry et al. (1995) reported a low incidence of adverse cardiac effects in a group of 8709 women treated with continuous terbutaline infusion. Overall, 47 (0.54%) had one or more cardiopulmonary problems. Pulmonary edema developed in 28 patients (0.32%), and 19 (0.22%) experienced other adverse cardiovascular effects, including ECG changes, irregular heart rate, chest pain, or dyspnea.

Lindenbaum et al (1992) examined the incidence of glucose intolerance in 37 patients using the subcutaneous terbutaline infusion pump compared with that of 54 patients receiving oral terbutaline and 634 control subjects without risk factors for gestational diabetes.
B. Risks of Subcutaneous Terbutaline Infusion Pump Maintenance Therapy, continued

The incidence of gestational diabetes was 5% in those using the subcutaneous terbutaline pump and 11% in those on the oral terbutaline vs. 6% in the control subjects (p = N.S. for both). Among those who had gestational diabetes, 100% of those using the pump and 50% of those on oral terbutaline required both insulin and diet compared to 8% of controls (p < 0.01 and p = 0.03, respectively). Thus, while the incidence of gestational diabetes was not increased in patients receiving terbutaline via the subcutaneous pump, the use of terbutaline significantly increased the need for insulin to achieve glycemic control in those who had gestational diabetes.

In 1997, the FDA sent a letter to physicians and other health care providers warning that adequate data establishing the safety and effectiveness of the use of terbutaline as a tocolytic agent had not been submitted to the FDA; that the demonstrated value of tocolytics was generally limited to an initial, brief period of treatment (≤ 48-72 hours); and that benefit from prolonged administration had not been documented. In addition, the letter noted that the safety of long-term subcutaneous administration of terbutaline, especially on an outpatient basis, had not been proven. The letter noted that complications of subcutaneous terbutaline therapy were similar to those accompanying its intravenous administration, including chest pain, tachycardia, dyspnea, pulmonary edema, and even death. Finally, the letter noted that the impact of long-term use of subcutaneous terbutaline on maternal glucose metabolism and of prolonged exposure of the fetus were still unknown (FDA, 1997).

**TA Criterion 4: The technology must be as beneficial as any established alternatives.**

Alternatives to maintenance tocolytic therapy with oral terbutaline or subcutaneous terbutaline infusion include bed rest, preterm labor education, weekly clinic visits, home uterine contraction self-assessment by manual palpation, daily phone contact, 24-hour perinatal nurse access (Rust et al., 1996).

Other tocolytic agents such as oral magnesium sulfate, oral ritodrine, and oral non-steroidal anti-inflammatory agents such as sulindac have been tried. Unfortunately, current evidence does not support improved pregnancy outcomes with these therapies (Maxwell, 2001).
TA Criterion 4, continued

For example, Chau and colleagues (1992) conducted a prospective, controlled comparison of intravenous then oral magnesium versus subcutaneous then oral terbutaline for tocolysis in 98 patients in preterm labor. Results showed that significantly more patients in the magnesium group delivered at ≥37 weeks: 73.9% versus 51.9% (p < .05). The interval between treatment and delivery was also greater for magnesium: 7.1 ± 3.9 weeks versus 5.0 ± 3.2 weeks (p < .005). The authors concluded that magnesium was associated with a higher term delivery rate. However, Ricci et al. (1991) conducted a prospective, randomized controlled study evaluating oral magnesium chloride versus oral ritodrine versus simple observation after successful intravenous magnesium sulfate tocolysis. Results showed that oral magnesium chloride was as effective as oral ritodrine, but neither was more effective than observation alone, in prolonging pregnancy and preventing recurrent preterm labor. Finally, a randomized, double-blind, placebo-controlled study of oral sulindac as maintenance therapy after successful parenteral tocolysis failed to reduce the incidence of readmission for preterm labor. There were no significant differences between the sulindac and control groups in time gained in utero, delivery at > 35 weeks' gestation, recurrent preterm labor, birth weight, or time spent in the neonatal intensive care unit (Humphrey et al., 2001).

TA criterion 4 is not met.

TA Criterion 5: The improvement must be attainable outside the investigational setting.

Subcutaneous terbutaline infusion pump tocolytic therapy has been studied in multiple centers. Whether it improves health outcomes from prevention of preterm birth has not been unequivocally demonstrated in the investigational setting. Whether it would improve health outcomes in the community setting under conditions of usual medical practice remains to be demonstrated.

TA criterion 5 is not met.
RECOMMENDATIONS OF OTHERS

Blue Cross Blue Shield Association (BCBSA)

The BCBSA Medical Policy Reference Manual (11/01/97) states,

“ Intravenous or subcutaneous terbutaline therapy may be considered medically necessary for the induction of tocolysis in patients with preterm (<37 weeks’ gestational age) labor.

Maintenance tocolytic therapy with either oral, subcutaneous or intravenous terbutaline is considered investigational.”

American College of Obstetricians-Gynecologists (ACOG)

1. ACOG’s Clinical Management Guidelines for Obstetrician Gynecologists (2001) states in part, “maternal tocolytic therapy may prolong pregnancy for up to 48 hours in some women, during which time corticosteroids can be administered. Because tocolytic and steroid therapy may result in untoward maternal and fetal consequences, use of these therapies should be limited to women with true preterm labor at high risk allows for appropriate maternal transport to a tertiary care center.”

2. ACOG representation at the meeting has been requested.

CONCLUSION

A. Oral Terbutaline Maintenance Therapy

Six randomized, placebo-controlled trials have examined the efficacy of maintenance oral terbutaline therapy in preventing recurrent preterm labor or preterm delivery among women who have successfully received parenteral intravenous tocolytic therapy for preterm labor. Five of these 6 trials found no benefit of the oral terbutaline compared to either placebo or no medication on either the preterm delivery rate or the mean interval between start of maintenance tocolytic therapy and time of delivery. The one randomized trial demonstrating a reduction in the rate of preterm delivery had several methodological flaws. In addition, these trials have not demonstrated a significant improvement in neonatal outcomes or birth weight with oral terbutaline maintenance therapy.
CONCLUSION, continued

B. Subcutaneous Terbutaline Infusion Pump Maintenance Therapy

Two prospective randomized, placebo-controlled trials of subcutaneous terbutaline infusion pump tocolytic therapy have been published. These trials demonstrated that subcutaneous terbutaline infusion pump tocolytic therapy was no more effective than oral terbutaline or saline placebo.

The side effects, potential toxicity, inconvenient dosing and likely noncompliance with oral terbutaline or subcutaneous terbutaline infusion by pump must also be considered. For example, there been occasional reports of serious maternal and fetal morbidity and even mortality, related to maintenance tocolytic therapy with terbutaline.

TA criteria 1, 3-5 are not met.

RECOMMENDATION

It is recommended that oral terbutaline as long-term maintenance tocolytic therapy does not meet Blue Shield TA criteria.

It is recommended that subcutaneous terbutaline infusion pump as long-term maintenance tocolytic therapy does not meet Blue Shield TA criteria.

Committee approval as recommended.

June 12, 2002
REFERENCES


REFERENCES, continued


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