Pharmacotherapy of Preterm Labor

Britt E. Travis, Pharm.D., and Jill M. McCullough, Pharm.D.

Preterm labor is defined as the onset of uterine contractions in a woman who has completed less than 37 weeks of pregnancy. It may be due to maternal, placental, fetal, or idiopathic causes, and it is associated with a number of risk factors. Nondrug measures such as bed rest and hydration have been used alone or in combination with drug therapy to treat the disorder. Pharmacologic (tocolytic) agents include ethanol, progesterone, indomethacin, nifedipine, β-adrenergic agonists, and magnesium salts. The three most commonly used drugs are ritodrine, terbutaline, and magnesium. (Pharmacotherapy 1993;13(1):28–36)

OUTLINE
Pathogenesis of Preterm Labor
Management—An Overview
Miscellaneous Agents
Ritodrine
Terbutaline
Magnesium
Comparative Trials
Conclusion

Pathogenesis of Preterm Labor

In approximately 50% of cases preterm labor has an idiopathic etiology. It may also be due to maternal, fetal, or placental factors; respectively, these are disease (e.g., pregnancy-induced hypertension, infection) and structural defects of the uterus or cervix; multiple gestations (e.g., twins, triplets) and abnormalities of the amniotic fluid (polyhydramnios, oligohydramnios); and placenta previa and abruptio placentae. In addition, various demographic, behavioral, and medical factors may place a woman at risk, such as inadequate prenatal care, a history of preterm labor or abortions, the use of alcohol or other addictive drugs, age (<17 or >35 yrs), race, and socioeconomic status. 

Management—An Overview

Before instituting any intervention for a woman with documented preterm labor, the risks and benefits of abating labor must be assessed. This requires evaluating fetal lung maturity, the status of the fetus (e.g., estimated weight, presence of fetal distress or anomalies, etc.), and the stage of labor. Uterine membrane status is also important. Patients with ruptured membranes, with or without uterine contractions, are at an increased risk of infection and it is less likely that their delivery can be delayed. The use of tocolytic therapy to prevent preterm birth in patients with ruptured membranes is controversial. Conversely,
tocolytics have been studied extensively in patients with intact membranes, and they may successfully delay delivery in many of these women. Depending on the status of the mother and fetus, the goal of tocolytic therapy may be to prolong gestation as long as possible, or simply to delay delivery for 48–72 hours (allowing for transport to an NICU).

Tocolytics are relatively contraindicated in women with mild chronic hypertension, hyperthyroidism, cardiac disease, or uncontrolled diabetes. These medical conditions may be exacerbated by the drugs, namely, β₂-agonists. Other relative contraindications are mild abruptio placentae, stable placenta previa, and fetal distress. Absolute contraindications include severe pregnancy-induced hypertension, severe abruptio placentae or bleeding from any cause, chorioamnionitis, severe fetal growth retardation, and fetal death.

Nondrug measures may be used, either as the only treatment or in addition to tocolytics. Bedrest is often recommended, although its effectiveness as sole therapy has not been substantiated. Hydration has also been used, but its efficacy in this setting has yet to be proved. Caution must be used when hydrating pregnant patients, because overhydration may increase the risk of adverse effects due to tocolytic drugs, namely pulmonary edema.

Miscellaneous Agents

Various mechanisms of action have been proposed to account for the effectiveness of tocolytic drugs. Some agents act directly on the myometrial cells to cause relaxation of the uterine muscle. Others decrease the amount of calcium available in myometrial cells, through a complex series of biochemical reactions, to produce relaxation.

Ethanol, once an agent of choice for the treatment of preterm labor, inhibits oxytocin secretion from the pituitary gland. Although it is sometimes effective, adverse effects such as maternal intoxication and a high frequency of respiratory depression in neonates are disadvantages to its use. Therefore, more effective drugs have replaced ethanol as first-line therapy to delay delivery.

Progestosterone affects myometrial gap junctions, which conduct electrical impulses through myometrial tissue. The result is a decrease in uterine muscle excitability. Because this effect develops over an extended period of time (up to 24 hrs), progesterone is often ineffective in treating preterm labor.

Isoxsuprine was the first β₂-agonist to be used in the United States to treat preterm labor. A few reports demonstrated some efficacy, but only one was a randomized, controlled trial. Isoxsuprine is seldom used because other β₂-agonists that have been more extensively studied are available, including ritodrine, which has received approval from the Food and Drug Administration (FDA).

Indomethacin inhibits the synthesis of prostaglandins, leading to decreases in free calcium levels and in myometrial muscle contraction. Limited numbers of controlled studies reported some success in treating preterm labor with indomethacin, prolonging gestation for at least 24 hours in most cases and up to 12 weeks in one; however, another group failed to demonstrate any significant gain in weeks of gestation. The major side effect of indomethacin is gastrointestinal upset, but it rarely warrants discontinue of treatment. Isolated case reports suggested that the drug may cause premature closing of the ductus arteriosus in the fetus, possibly leading to primary pulmonary hypertension in the newborn. However, the complications of prematurity (infection, respiratory distress syndrome, etc.) make it difficult to determine if indomethacin is directly responsible. In addition, its effects on platelet aggregation and its ability to mask temperature elevations could complicate pregnancy if severe bleeding occurs during delivery or if infection is present. These concerns have limited the agent’s use for the treatment of preterm labor.

Nifedipine shows some promise as a tocolytic. It inhibits the movement of calcium into smooth muscle, thereby blocking the interaction between contractile proteins and preventing myometrial contractions. Dosages typically are 20 mg 3 times/day. Treatment for as few as 3 days resulted in a delay of delivery for a mean of 14 days in one report and 36.3 days in another. Side effects are minimal, the most common being facial flushing; headache and increased pulse rate have also been reported. Due to its apparent efficacy and lack of significant side effects, nifedipine may be valuable in this setting, but larger trials are necessary to define its role.

Ritodrine

Ritodrine hydrochloride, an adrenergic agonist with selective β₂-receptor activity, is currently the only FDA-approved agent for the treatment of preterm labor. It binds to β₂-receptors located on the outer surface of the myometrium, triggering the conversion of adenosine 3′,5′-monophosphate (cAMP). As a result, the activity of the sodium-potassium pump is increased, creating a gradient that accelerates the rate of sodium and calcium exchange, which leads to an increase in the amount of calcium that is pumped out of the myometrial cells. Decreased intracellular calcium


PHARMACOTHERAPY OF PRETERM LABOR Travis and McCullough 29
causes a decrease in the combining of actin and myosin, and a decrease in muscle contractions. The result is relaxation of myometrial tissue.\textsuperscript{34} Ritodrine may also act on the trophoblast, a structure that eventually becomes part of the placenta. In this tissue, $\beta_2$-agonists increase cAMP leading to increased production of placental progesterone.\textsuperscript{35} Progesterone acts to decrease the number of myometrial gap junctions and thus inhibits uterine contractions.\textsuperscript{35}

Ritodrine can be administered orally or by intravenous infusion. Intramuscular injection is undesirable due to difficulties in dose titration and pain on injection.\textsuperscript{36} Subcutaneous injection is not recommended because the volume of fluid necessary to deliver a dose cannot be given subcutaneously. Oral ritodrine undergoes significant first-pass metabolism, which results in bioavailability of approximately 30%.\textsuperscript{33,37}

The manufacturer recommends an initial intravenous infusion of 100 $\mu$g/minute, with increases of 50 $\mu$g/minute every 10 minutes to a maximum of 350 $\mu$g/minute. The rate should be increased until contractions cease, and then maintained for at least 12 hours.\textsuperscript{33} A modified protocol that aims to minimize side effects and fluid overload is 50 $\mu$g/minute initially, with increases of 50 $\mu$g/minute every 20 minutes to a maximum of 350 $\mu$g/minute.\textsuperscript{35} Once contractions have stopped, the infusion rate is maintained for 1 hour and then is decreased by 50 $\mu$g/minute every 30 minutes to the lowest rate that inhibits uterine activity (no lower than 50 $\mu$g/min). This maintenance rate is continued for 12 hours. If labor recurs, the entire protocol is repeated.

Dosage adjustments should be made according to maternal effects as well.\textsuperscript{34} If the maternal heart rate is greater than 140 beats/minute, the dosage of ritodrine should not be increased further; if the patient is symptomatic the dosage should be decreased.

Ritodrine solutions are prepared by diluting 150 mg of drug in 500 ml 5% dextrose for a final concentration of 0.3 mg/ml.\textsuperscript{33} Normal saline may be used when treating diabetic patients, and more concentrated solutions may be prepared if fluid restriction is necessary.\textsuperscript{33}

Oral ritodrine is usually started 30 minutes before the infusion is discontinued.\textsuperscript{33,34} The initial dosage is 10 mg every 2–4 hours for 24 hours, and then 10–20 mg every 4–6 hours until ritodrine is no longer needed.\textsuperscript{1,33,34} During the initial 24 hours, the more frequent schedule is often employed.\textsuperscript{37} Adjustments are guided further by patient response and adverse effects. The maximum recommended daily dose is 120 mg.\textsuperscript{33}

Ritodrine is relatively specific for $\beta_2$-receptors; however, receptors in the heart, bronchi, and other tissues are structurally similar to those in the uterus, thus increasing the chance of adverse effects. As a result, maternal heart rate and contractility increase when the drug is administered.\textsuperscript{38,39} This effect can be additive to the already volume-overloaded, hyperdynamic cardiac state of a pregnant woman.\textsuperscript{10}

Intravenous ritodrine was associated with palpitations in one-third of all patients studied in the United States.\textsuperscript{34} Other reported cardio-pulmonary events with this and other $\beta$-agonists are hypotension,\textsuperscript{40} chest pain,\textsuperscript{34,42} shortness of breath,\textsuperscript{34,40} angina pectoris,\textsuperscript{41} myocardial ischemia,\textsuperscript{42} and cardiac arrhythmias.\textsuperscript{43}

Pulmonary edema has been associated with the use of $\beta$-agonists.\textsuperscript{35,42-46} Perhaps due to iatrogenic fluid overload or to fluid retention secondary to decreased urinary sodium and water loss caused by the drugs, multiple gestation appears to be a risk factor for the development of pulmonary edema.\textsuperscript{42,46} The concomitant use of corticosteroids to promote fetal lung maturity also is proposed as a risk factor, although pulmonary edema has been reported in patients receiving $\beta$-agonists without simultaneous steroid therapy. Moreover, the corticosteroids most commonly used in preterm labor (betamethasone, dexamethasone) have little if any mineralocorticoid activity.

Due to the effect of $\beta_2$-agonists on glycogenolysis and gluconeogenesis in the liver and skeletal muscle, maternal serum glucose concentrations increase with ritodrine administration.\textsuperscript{38} This increase occurs early in therapy and may resolve without intervention or gradually decrease toward normal with continued treatment.\textsuperscript{38,47} Diabetic patients may have a significantly greater increase than nondiabetic patients and thus they are at risk of developing diabetic ketoacidosis; insulin may be required to control their blood glucose.\textsuperscript{35,38} Blood glucose levels should be monitored in all patients receiving ritodrine,\textsuperscript{35} with appropriate interventions initiated as needed.

Changes in serum levels of triglycerides, free fatty acids, and other lipids may occur with ritodrine, but these effects usually resolve within 24 hours.\textsuperscript{38} Transient hypokalemia is frequent, but replacement therapy is rarely warranted because total-body potassium usually remains normal.\textsuperscript{10} Nausea, headache, nervousness, and anxiety can also occur.\textsuperscript{34}

Ritodrine crosses the placenta.\textsuperscript{45} Fetal adverse effects are similar to those seen in the mother, but may occur less often because fetal drug concentrations are usually lower than maternal levels.\textsuperscript{49} A mean maternal:fetal ratio of serum ritodrine was reported to be 1.17 ± 0.48.\textsuperscript{49}

Fetal heart rate may increase or decrease, but the change is usually not clinically significant.\textsuperscript{50} Neonatal hypoglycemia may result from maternal hyperglycemia and hyperinsulinemia.\textsuperscript{50} The hypoglycemia may be most pronounced if ritodrine
Continuous subcutaneous infusions using a modified miniature pump (terbutaline pump therapy) have also been used to treat preterm labor. Tocolytic failure is often associated with intravenous or oral treatment, and is thought to be due to $\beta_2$-receptor down-regulation. Lower total daily subcutaneous doses may prevent the down-regulation and thus tocolytic failure. It is also believed that a basal infusion can control uterine irritability, therefore preventing the development of uterine contractions. Effective total daily doses of terbutaline using this mode of administration range from 2–4 mg.

Preterm labor was treated successfully in nine outpatients using a subcutaneous infusion pump containing terbutaline 3 mg in a 3-ml reservoir. 

Patients received an initial infusion of 50 $\mu$g/hour, with boluses of 240 $\mu$g as needed during periods of increased uterine activity. Delivery was delayed an average of 9.2 ± 4.3 weeks, and only one patient experienced tocolytic failure, requiring stabilization with intravenous magnesium sulfate. She was then discharged with terbutaline pump therapy, and delivered during the thirty-eighth week of pregnancy.

The advantage of the outpatient subcutaneous pump is threefold: the total daily dose of terbutaline is much lower than typical daily intravenous or oral doses; it does not require large volumes of fluid, as intravenous infusions do, which reduces the risk of fluid overload; and patients do not have to be hospitalized to receive therapy. However, terbutaline pump therapy is more expensive than oral tocolysis and requires intensive home monitoring. Comparative efficacy studies of terbutaline pump therapy and intravenous or oral regimens have not been published to date.

Terbutaline, like ritodrine, is not specific for uterine muscle. During intravenous infusions, the most common adverse effects are tachycardia, tremor, palpitations, shortness of breath, and dizziness. Adverse cardiovascular effects caused termination of therapy in up to 10% of patients. As with ritodrine, patients must be monitored closely for the development of cardiac arrhythmias or pulmonary edema.

Moderate increases in serum glucose concentrations have been noted during terbutaline infusions. The concentration generally remains elevated throughout the infusion, but returns toward normal after treatment is stopped. A corresponding increase in serum insulin is also seen. Therefore, as with ritodrine therapy, caution should be used when administering terbutaline to pregnant patients with diabetes, and serum glucose levels should be monitored in all patients.

Transient hypokalemia occurs in some patients receiving terbutaline, with little effect on serum
sodium, creatinine, or phosphorus. The hypokalemia is most likely due to intracellular movement of potassium in response to increased insulin secretion. A significant increase in serum lactate has also been reported. Some patients experience vomiting during drug infusion, which may contribute to the metabolic changes.

Subcutaneous administration causes fewer adverse reactions than intravenous and oral therapy because lower total daily doses are used. In one report, a total of 394 patient days were reviewed in nine patients receiving subcutaneous terbutaline pump therapy. No cardiac or electrolyte abnormalities were reported. The mean maternal pulse rate was 88 ± 12 beats/minute. However, bolus injections did cause transient increases in maternal pulse rate. In a larger chart review of 70 patients, one patient experienced anxiousness and shortness of breath after an intermittent subcutaneous dose, which resolved on discontinuation of therapy.

Terbutaline crosses the placenta, and therapeutic levels can be achieved in the fetus. In a study of 14 healthy pregnant women, the average umbilical cord blood concentration:maternal vein concentration was 0.36 ± 0.15 after a single injection of 250 μg. Fetal tachycardia may occur during intravenous infusions. Infants born to terbutaline-treated mothers appear to be developmentally and neurologically equivalent to those who were not exposed to the drug in utero.

Fetal glucose levels tend to parallel maternal levels. Some infants may have a high insulin level at birth, but it does not appear to correlate with terbutaline administration. Newborns also may experience hypoglycemia, especially if the mother received combination terbutaline-steroid therapy.

**Magnesium**

Magnesium inhibits uterine contractions by decreasing the release of acetylcholine at the neuromuscular junction, thus decreasing the amplitude of electrical signals in myometrial cells. Increased intracellular magnesium also leads to increased cAMP concentrations, resulting in an increase in the amount of calcium that is pumped out of the myometrial cells. In addition, magnesium may prevent the entry of calcium into myometrial cells. The interaction of contractile proteins, and therefore muscle contraction, does not occur in the presence of low intracellular calcium.

Magnesium may be administered by the intravenous or oral route. As with the β2-agonists, numerous dosing protocols exist for the treatment of preterm labor. Intravenous magnesium sulfate is generally given as a loading dose of 4–6 g over 20 minutes, followed by a maintenance infusion of 2–3 g/hour and continued for 12–24 hours if it is successful. Maintenance infusions as high as 4 g/hour have been administered in some cases. The loading dose is prepared by diluting magnesium sulfate 4 g in 250 ml 5% dextrose or 0.9% sodium chloride solution. The maintenance solution contains 20–40 g in 500–1000 ml diluent. Serum magnesium levels should be measured within 6 hours of the start of the infusion.

Once contractions have stopped, magnesium oxide or gluconate 250–500 mg is administered orally every 3 hours. Due to erratic absorption of these salts and the potential for significant diarrhea, some clinicians favor the use of an oral β2-agonist after intravenous magnesium. Another protocol employs the same intravenous and oral dosing schemes, but also stresses the importance of monitoring fluid status, respiratory function, and reflexes throughout treatment.

Fewer adverse effects occur with magnesium than with β2-agonists, and can be predicted based on serum magnesium levels. Reflexes are lost at levels of 12 mg/dl (10 mEq/L), respiratory depression can occur at 14–18 mg/dl (12–15 mEq/L), and cardiac arrest is possible at levels above 18 mg/dl (15 mEq/L).

According to a retrospective review, only 24 of 355 patients treated with intravenous magnesium sulfate experienced adverse effects, and only 7 of them had to discontinue treatment. The most common adverse effects were nausea and/or flushing, which were similar to those reported in another study. Chest pain, chest tightness, drowsiness, and blurred vision were also reported. Four patients experienced pulmonary edema, necessitating discontinuation of therapy. General muscle weakness, respiratory depression, and hypotension led to the discontinuation of a magnesium infusion in one report. Diarrhea has been reported with oral magnesium and may prevent its use. Metabolic effects, such as hypokalemia and hyperglycemia, are rare, and thus magnesium may be a safer agent than the β2-agonists for the management of preterm labor in diabetic patients.

Magnesium freely crosses the placenta. Infants with defective bone formation and rickets have been born to women treated with long-term intravenous magnesium sulfate tocolysis. In one report the abnormality resolved postnatally. One group observed no significant changes in fetal tone, amniotic fluid volume, or body movements in infants born to mothers treated with magnesium sulfate. They did, however, note a decrease in fetal heart rate.

**Comparative Trials**
Numerous clinical trials have been conducted to assess the efficacy of the various drugs in the treatment of preterm labor. The data generated by these trials are often difficult to interpret and compare due to differences in study design, definitions of preterm labor, inclusion and exclusion criteria, routes of drug administration, and the dosages of agents. The following is a review of some of the randomized comparative trials that were conducted with ritodrine, terbutaline, and magnesium. They were similar with respect to inclusion and exclusion criteria, drug dosages, and routes of administration, which should assist the reader in understanding how the agents compare to one another.

A prospective, randomized, double-blind trial compared the intravenous and oral forms of ritodrine and terbutaline. All patients received an intravenous infusion of either ritodrine 50–350 µg/minute, titrated to the lowest effective dosage, or terbutaline 2.5–17.5 µg/minute, titrated to the lowest effective dosage, for 12 hours. Patients with intact membranes were then switched to oral therapy with their respective drug—ritodrine 20 mg or terbutaline 5 mg every 4 hours for 5 days. Both agents effectively suppressed uterine contractions during intravenous infusion. However, patients who received oral ritodrine experienced significantly more episodes of recurrent preterm labor (12/23 patients) than those receiving oral terbutaline (1/19; p<0.001). In the former group, 8 of the 12 patients experiencing recurrent labor delivered during the initial hospitalization, whereas 15 of the 23 without a recurrence were discharged without delivering, and 6 of them did not deliver until after 36 weeks of pregnancy. The patient who experienced recurrent preterm labor while receiving oral terbutaline did not deliver as a result of that episode. Twelve of the remaining 19 patients treated with terbutaline did not deliver until after 36 weeks of pregnancy. Adverse effects during the infusion period were comparable between groups. Patients receiving ritodrine suffered more tachycardia, and those receiving terbutaline more often experienced hyperglycemia. These results suggest that both agents are equally effective when given intravenously, but terbutaline may be a better choice for oral therapy to prevent recurrent preterm labor.

Patients in preterm labor with intact membranes were randomized to receive an intravenous loading dose of magnesium sulfate 4 g, then 2 g/hour for 2 hours and 1 g/hour for 22 hours, or terbutaline 250 µg loading dose, then 10–25 µg/minute, titrated to the lowest effective dosage, for 22 hours. Both groups of patients also received a single 5-mg oral dose of terbutaline 20 hours after the magnesium or terbutaline loading dose. The success rate, defined as delay of delivery for at least 24 hours, was similar for both agents: 64% (9/14) for magnesium, and 67% (10/15) for terbutaline. Fifty-seven percent of patients receiving magnesium and 53% receiving terbutaline were able to postpone delivery until after 37 weeks’ gestation. There were no clinically significant side effects with the magnesium sulfate infusion. However, five patients in the terbutaline group discontinued treatment due to chest pain, shortness of breath, or nausea and vomiting. Thus, although both agents had similar success rates, magnesium sulfate was favored as a first-line agent due to the lack of adverse effects during the infusion period. It is difficult to interpret the results of this study fully, however, because the single oral dose of terbutaline does not reflect what is currently common practice (i.e., oral therapy until 37 weeks’ gestation).

In another study, seventy patients were randomized to receive an infusion of ritodrine 100–350 µg/minute, titrated to the lowest effective dosage, for 12 hours or magnesium sulfate 4 g loading dose, followed by 2 g/hour continuous infusion, titrated to achieve levels of 6–8 mg/dl, for 12 hours. Participants who failed to respond to one agent were treated with the other agent, and those who failed both drugs were withdrawn from the study. Those who responded to either drug were switched to oral ritodrine 10 mg every 2 hours for 24 hours, then 10 mg every 4 hours until 37 weeks’ gestation. Patients without insurance received oral terbutaline 5 mg every 4–6 hours until 37 weeks’ gestation due to the lower cost; this did not appear to have any impact on the outcome of the study. Thirty-six patients received ritodrine first, and three received ritodrine after magnesium sulfate failed to stop labor. Thirty-four patients received magnesium sulfate first, and six received magnesium sulfate after ritodrine failed to stop labor.

As a first- or second-line agent, ritodrine successfully delayed labor for at least 72 hours in 31 (79%) of 39 patients, and for 1 week or more in 28 (72%) of 39 patients. Magnesium sulfate as a first- or second-line agent delayed labor for at least 72 hours in 35 (88%) of 40 patients, and for 1 week or more in 30 (75%) of 40 patients. No information about delaying delivery until 37 weeks’ gestation was reported. The time required to achieve uterine quiescence was significantly shorter for patients receiving ritodrine (mean 1.56 hrs vs 3.3 hrs for patients receiving magnesium sulfate; p<0.05). However, patients receiving magnesium sulfate did not experience any progressive cervical changes during this time period. The frequency of adverse effects was similar for both groups (38 reports in the ritodrine group vs 33 reports in the magnesium sulfate group). Patients receiving ritodrine experienced hypokalemia, hyperglycemia, nausea, and cardiac side effects, whereas the patients receiving magnesium sulfate experienced lethargy,
nausea, dry mouth, dizziness, and nystagmus. Two patients receiving ritodrine had to discontinue therapy due to tachycardia, and two patients receiving magnesium sulfate required a decrease in dosage due to lethargy, but did not have to discontinue treatment.

These results suggest that ritodrine may be a better choice for the treatment of preterm labor due to its more rapid suppression of uterine activity, which can help to relieve some of the anxiety associated with the disorder. Magnesium sulfate may also be considered a drug of choice because it usually does not cause serious cardiac side effects. Also, serum magnesium levels can be used in making dosage adjustments, due to the close relationship between serum levels and tocolysis.

In a prospective trial, 50 patients were randomized to receive either oral terbutaline 2.5–5 mg every 3–4 hours, or oral magnesium oxide 200 mg every 3–4 hours after successful intravenous tocolysis. Patients continued oral tocolysis until the thirty-sixth week of gestation. Estimated gestational ages at entry and delivery were comparable between the two groups. Adverse effects of terbutaline included palpitations, tachycardia, shaking, and nervousness. The primary adverse effects of magnesium oxide were diarrhea, nausea, and vomiting. Recurrence of preterm labor was similar for both drugs: 11 episodes in patients receiving terbutaline, 13 episodes in patients receiving magnesium oxide.

Magnesium oxide may be a rational choice for long-term oral tocolysis because it is less expensive than oral terbutaline, but it may cause diarrhea. One must interpret the results of this study cautiously because the initial intravenous tocolytic therapy, which was not reported, may have affected the outcome.

In another randomized trial, 45 patients received ritodrine 100–350 μg/minute, 40 received terbutaline 20–70 μg/minute, and 46 received magnesium 1.5–3.5 g/hour after a 4-g loading dose. All agents were administered as a continuous infusion that was continued for 12 hours after contractions had stopped. Patients who failed to respond or could not tolerate the adverse effects of one class of agent were switched to the other class. Both classes were equally effective in delaying delivery for at least 48 hours, although more patients treated with magnesium sulfate experienced persistent contractions. The number of days gained in utero was not significantly different between the β-agonists and magnesium sulfate (ritodrine 43 ± 25 days, terbutaline 55 ± 17 days, magnesium 38 ± 27 days).

It is difficult to interpret these results, however, because each patient was switched to oral terbutaline 2.5 mg every 4 hours at the end of the infusion. Successful outcomes may have been the result of the long-term oral treatment rather than the initial tocolytic agent. As in other trials, the β-agonists caused more adverse effects, mainly cardiovascular. This led to a number of treatment failures because patients could not tolerate effective dosages of ritodrine or terbutaline.

Conclusion

In general, patients experiencing preterm labor are initially stabilized with an intravenous agent, and then treated until 37 weeks of gestation with an oral tocolytic drug. Although few data support long-term oral tocolytic therapy (i.e., until 37 wks of pregnancy), it is a common practice.

In otherwise healthy patients, intravenous magnesium sulfate is considered to be the drug of choice in treating preterm labor. It is easy to administer and has fewer adverse effects than ritodrine or terbutaline. If the contractions have been inhibited for 12–24 hours with intravenous magnesium sulfate, the patient is given an oral tocolytic. Terbutaline is usually the oral agent of choice because it is cheap and appears to be as effective as ritodrine. The efficacy of oral magnesium oxide and gluconate has not been established. If the patient fails to respond to intravenous magnesium sulfate, intravenous ritodrine is administered according to the manufacturer's guidelines, followed by oral terbutaline.

Cardiac disease is an absolute contraindication to the use of ritodrine and terbutaline due to the cardiac side effects of these drugs. Thus, magnesium sulfate is the agent of choice in these patients. It is also preferred for diabetic patients. However, the effects of ritodrine and terbutaline on serum glucose can be managed with insulin. Diabetes is therefore considered a relative contraindication to treatment with the β-agonists.

Patients who have failed standard therapies at least once may be candidates for subcutaneous terbutaline pump therapy. However, this method is more expensive than oral terbutaline, and requires significant patient involvement. If a patient fails subcutaneous terbutaline pump therapy, intravenous magnesium sulfate followed by oral terbutaline may be tried again. It is thought that treatment with magnesium allows for the regeneration of β₂-receptors, and subsequent successful tocolysis with an oral β₂-agonist.

Despite the development of effective tocolytic drugs and an increase in their use, preterm labor is still a significant health problem in the United States. Thus, in addition to the search for new agents that are effective, safer, and easier to use, efforts must be focused on preventing preterm labor. Adequate prenatal care must be made available to all women, and those at risk for
preterm labor should receive additional attention. Finally, all health care professionals should be educated about preterm labor and their role in preventing and treating this unfortunate complication of pregnancy.

References