

Atosiban: Perspectives On The Etiological Management of Preterm Labor

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Abstract

We analyzed the information available about the tocolytic drug atosiban to evaluate the advantages and disadvantages of this drug compared to first line tocolytics regarding fast inhibition of uterine contractions, prolongation of pregnancy and maternal, fetal and neonatal adverse effects. Eleven articles of preclinical topics and eight clinical studies were analyzed; four of them are randomized placebo controlled trials. We concluded that atosiban is comparable to β -agonists in delaying labor for up to 7 days without significant prolongation of pregnancy or reduction of perinatal morbidity and mortality. Atosiban is better tolerated than β -agonists, however its short and long term safety for the mother and fetus is still unproved, thus we suggest its use should be considered only after failure of standard therapy of premature labor.

INTRODUCTION

Preterm birth is the single most important cause of perinatal morbidity and mortality, excluding lethal congenital malformations. It is responsible for 75% of all perinatal deaths and for 50% of neurological disabilities in childhood. Diagnosis of preterm labor is based in the presence of coordinated and frequent uterine contractions (6 in 30 minutes) and cervical changes (effacement >50% and dilatation >1cm.) in a gestation of less than 37 weeks. In nearly 50% of patients' contractions stop spontaneously during observation; but if contractions persist, cervical changes became progressive and there is no contraindication for tocolysis, the patient should receive a drug to inhibit uterine contractions (1).

However, despite the increasing knowledge in uterine smooth muscle physiology and pharmacology, the preterm labor/delivery rate has remained stable in the last 30 years.

Lastly growing evidence suggests that pPreterm labor is a syndrome, that is the clinical manifestation of many etiologies (2). Nevertheless our therapeutic approach does not differentiate between the probable etiologies of premature contractions and we always administer the same drug to every patient. It is possible that this action may explain the frequent failure of this treatment and the incapacity of tocolytic drugs to significantly prolong pregnancy.

The perfect tocolytic would be one that, being safe for mother and fetus, could prolong gestation for enough time to achieve a significant reduction of preterm birth, allowing fetal maturation and therefore diminishing perinatal morbidity and mortality. However, the tocolytics available at present do not fulfill these requirements (3,4). It has been demonstrated its ability to significantly delay labor for up to 48 hours, useful to induce lung maturation with corticoids, but they did not produce a significant reduction of prematurity rate. Furthermore, they have frequent side effects that cause maternal and fetal morbidity and high rates of withdrawal, especially the β -agonists (first line drugs) (1). Currently, there is four main tocolytic drugs: β -agonists (ritodrine, terbutalina, fenoterol), magnesium sulfate, indomethacin and calcium channel blockers. However the evidence clearly shows that none of them achieve a consistent prolongation of gestation (deeply reviewed in reference 1).

Atosiban, a new tocolytic, will soon be available worldwide, it is a specific oxytocin receptor antagonist that is already being used in Europe and Canada but not approved by the FDA. In the last years many clinical trials have been followed to evaluate its efficacy and safety. The objective of this review is to critically analyze appraise the information available on atosiban to evaluate the quality of the evidence on the advantages and disadvantages of this drug compared to the usual tocolytics regarding: fast inhibition of uterine contractions, prolongation of pregnancy and adverse effects

in the mother, fetus and newborn. The information collected would allow us to determine the usefulness of this drug in the management of preterm labor.

PRECLINICAL ANTECEDENTS

We searched MEDLINE for studies between January 1992 and January 2002, using the terms “atosiban” and “antocin®”. We also included as secondary references the articles cited in the primary articles because of its relevance or frequent citation. We considered 11 preclinical articles (in vitro studies, animal models and pharmacology) and 8 clinical trials, 4 of them are clinical randomized controlled trials.

Atosiban is a synthetic 9 amino acid peptide that corresponds to the oxytocin molecule modified in positions 1,2,4 and 8. It is a competitive inhibitor that binds the oxytocin receptor in the myometrium and decidua preventing the action of oxytocin in the target cells. Oxytocin activates phospholipase C by binding to its receptor in the cellular membrane of the smooth muscle cell, increasing inositol phosphate and intracellular calcium, thus leading to uterine contraction. In the decidua the binding of oxytocin to its receptor produces prostaglandin release, mainly PGF₂, thus increasing in the number of gap junctions and producing a greater sensitivity to oxytocin in the underlying myometrium (3). Therefore the competitive binding of atosiban to the oxytocin receptor may prevent the uterotonic action of oxytocin on the myometrium and prostaglandin release by the decidua.

In vitro studies show that atosiban specifically inhibits oxytocin-induced contractions. In vivo, atosiban inhibited induced and spontaneous uterine contractions in a dose dependent way, delayed progression of labor and inhibited milk ejection (6,7,8,9,10). Pharmacokinetics studies in pregnant women showed a half-life of 18 ± 3 minutes, clearance of 42 L/hr and a distribution volume of 18 liters (11). The drug transfer across the placenta in term pregnancies was minimal (12%) and did not increase during longer infusion (12).

CLINICAL STUDIES

Descriptive studies showed a reduction in uterine activity during atosiban infusion in patients with preterm labor (13, 14). The first randomized controlled trial in humans showed a significant reduction in the frequency of contractions compared to placebo; there were no difference in blood pressure or heart rate during the infusion (15). The minimum effective dose was determined later by comparing different

doses of atosiban with ritodrine (β-agonist) and the effect of the administration of an initial bolus (0.6 mg-6.5 mg), concluding that the most effective dose was a 6.5 mg i.v. bolus followed by a continuous infusion of 300µg/min (16).

We evaluated four prospective, double blind, randomized, and controlled trials. They compared atosiban with placebo (as acute and maintenance treatment) and with the β-agonists ritodrine and terbutaline (17,18,19,20). The objective of the four studies was to evaluate the efficacy and safety of atosiban in the treatment of preterm labor and their designs were similar (multicentric, double blind, randomized, placebo controlled trials). The randomization was computer-generated allocating and stratifying by center in all studies, and also by gestational age in the studies that compared with β-agonists. The efficacy was analyzed by intention to treat and the safety according to the drug that the patient in fact received. Patients included were those in preterm labor with intact membranes, cervical dilatation of = 3cm, between 20 to 33+6 weeks (in the placebo trial) and between 23 to 33+6 (in the trial that compared atosiban with β-agonists). Atosiban was administered as 6.75 mg i.v. bolus over 1 minute, followed immediately by infusion of 300µg/min for 3 hours, then 100µg/min for up to 45 hours. Maintenance therapy began as subcutaneous infusion pump that provided continuous atosiban infusion of 6ml/h (30µg/min), these patients were discharged from hospital with the ambulatory treatment until 36 weeks. In cases where labor progressed patients received rescue tocolysis, after at least 1 hour of observation during intravenous treatment.

1. Atosiban vs. placebo with tocolytic rescue. The first trial compares atosiban with placebo in the management of preterm labor (17). A total of 246 patients were randomized to receive atosiban and 246 to placebo; the primary endpoint was the time from the start of study drug to delivery or therapeutic failure. Secondary end points were the proportion of patients who remained undelivered and did not receive an alternative tocolytic at 24 hours, 48 hours and 7 days; maternal, fetal and neonatal side effects were also evaluated. The study showed that both groups were comparable in most of the prognostic variables, except in mean gestational age on admission, that was significantly greater for the placebo group. The atosiban group had a greater proportion of patients with less than 28 weeks on admission (17% atosiban group vs. 13% placebo group; $p < 0.05$). No significant difference was found in the time from start of treatment to delivery or therapeutic failure (25.6 days with atosiban and 21 days with placebo).

The proportion of patients that remained undelivered and not requiring an alternative tocolytic at 24, 48 hours and 7 days was significantly higher in the patients who received atosiban and had a gestational age on admission of more than 28 weeks, however there was no difference for the ones with less than 28 weeks on admission. Rescue tocolysis was administered to 42% of the women on atosiban and 51% on placebo ones (no difference). There was no difference in the number of preterm deliveries (58% vs. 51% atosiban vs. placebo), birth weight, newborns admitted to intensive care units (42% vs. 38%), respiratory distress syndrome (23% vs. 18%) or intracranial hemorrhage (7% vs. 8%). The fetal-infant mortality rate was higher in the atosiban group (4.5% vs. 1.7%; $p<0.05$), mainly related to extreme prematurity. There were no maternal deaths. The incidence of adverse effects in both groups was comparable (thoracic pain, tachycardia and fetal distress) except for injection site reaction that was higher in the atosiban group. Around 4% of the placebo patients and 16% of the atosiban patients discontinued the therapy because of adverse effects.

Comments: Despite the good design of this trial, there was a randomization bias because they did not perform stratified randomization by gestational age on admission, generating groups that were not comparable in that feature (atosiban group had twice as many patients with gestational age of less than 26 weeks). The authors consider that the higher morbidity and mortality in the atosiban group was secondary to a greater number of extreme preterm newborns, however we judge it is not possible to be completely confident that the higher morbidity and mortality in the atosiban group is just exclusively because of prematurity. In the study design they did not establish as a subject of analysis by dividing in groups of more or less than 28 weeks, invalidating conclusions obtained by this secondary analysis, we appraise they can only be considered as hypothesis for future trials. The outcomes are very relevant, but difficult to measure because of the presence of false preterm labor, showed by a 49% of patients in the placebo group that did not need rescue therapy. Another difficulty was ethical, thus comparison to placebo was only for one hour and rescue treatment was administered if preterm labor progressed, besides apparently many patients received rescue drugs before they fulfill the failure criteria.

2. Maintenance treatment with atosiban. The second trial evaluated the utility of maintenance treatment with atosiban in women with preterm labor who achieved successful tocolysis with i.v. atosiban (18). A total of 512 patients who

inhibit uterine contractions with i.v. atosiban were included, and randomized to maintenance atosiban (261) or placebo (251). The primary outcome was the number of days from the start of maintenance therapy until the first recurrence of labor. Secondary end points were the percentage of patients receiving subsequent i.v. atosiban therapy and maternal and fetal side effects.

The time (median) from the start of maintenance treatment to the first recurrence of labor was significantly longer in the atosiban group (32.6 days vs. 27.6 days; $p=0.02$). There was no difference in the number of patients who required subsequent i.v. atosiban therapy. The adverse effects in both groups were comparable except for injection site reactions that were more common in the atosiban group (70% vs. 48%; $p<0.0001$). Subcutaneous injection site reaction was the leading cause of discontinuation of therapy in both maintenance groups.

Maternal-infant outcomes were comparable; there were 10 fetal or infant deaths; 5 in the placebo maintenance group and 5 in the atosiban maintenance group. There were no differences in the number of preterm deliveries (34% vs. 38%; atosiban vs. placebo), birth weight, newborns admitted to intensive care units (21% vs. 26%; atosiban vs. placebo), respiratory distress syndrome (11% vs. 11%) or intracranial hemorrhage (6% vs. 4%; atosiban vs. placebo).

Comments: The protocol is methodologically correct, but its external value is limited by the requirement of the patients to have responded to i.v. treatment with atosiban. Thus the efficacy of maintenance tocolysis with atosiban is proved for patients who have already responded to this drug in the acute episode, and not to other tocolytic drug. The primary outcome is very simple and easy to measure, but is not quite relevant. Regarding perinatal outcome however, the frequency of preterm birth and perinatal morbidity or mortality were not different.

3. Atosiban vs. β -adrenergic drugs. The other two randomized trials compared the efficacy and safety of atosiban with ritodrine (19) and terbutaline (20). From 247 patients, 128 were randomized to atosiban and 119 to ritodrine. And from 249 patients, 116 were randomized to atosiban and 133 to terbutaline. As primary end points the authors measured the proportion of women undelivered without use of an alternate tocolytic after 48 hours and 7 days, maternal side effects (especially cardiovascular) and neonatal outcomes. Secondary end points were: change in contraction rate with time, mean gestational age at delivery,

proportion of infants born at < 1500g and 1500-2500g, and the number of infants requiring neonatal intensive care.

In the trial that compared atosiban with ritodrine both groups were not comparable because of the absence of stratification for multiple pregnancies. Having 19% of multiple pregnancies (39 infants) in the atosiban group and 14% (29 infants) in the ritodrine group. None of the two studies showed a difference in the total number of women that did not deliver at 48 and 72 hours after initiating treatment. In the study that compared atosiban with ritodrine there was a significant difference in the proportion of patients that had not delivered nor had required an alternative drug 7 days after treatment (64.3% with atosiban vs. 52.9% with ritodrine $p=0.03$ OR 1.85 IC 1.06-3.21); there was no difference when compared to terbutaline. A greater number of adverse effects was reported with β -agonists, especially tachycardia (74% vs. 1% comparing with ritodrine and 75.2% vs. 4.3% comparing with terbutaline), which led to a greater withdrawal of treatment (30% vs. 0.8% comparing with ritodrine and 13,2% vs. 1.7% comparing with terbutaline) . There was one severe maternal complication; a patient that received treatment with ritodrine developed pulmonary edema, probably associated with drug use.

The perinatal outcome was comparable in the different treatment groups. There were no differences in gestational age at delivery/birth, birth weight, and proportion of newborns that required hospitalization in an intensive care unit or developed respiratory distress or intracranial hemorrhage. Globally the perinatal adverse effects were comparable, even though the respiratory problems (respiratory distress syndrome and apneas) were more frequent in multiple pregnancies that received atosiban compared to ritodrine.

Comments: As we previously mentioned, this study has a selection bias since there is a greater distribution of multiple pregnancies in the group treated with atosiban. This coincides with worse perinatal results in the multiple pregnancies that received atosiban. Another issue is that they were not able to maintain an adequate double blind due to the evident cardiovascular effects of the β -agonists, which could have led to an intervention bias.

Summary of results: The information presented in these four double blind, randomized, prospective, controlled trials may be summarized as follows:

1. Atosiban compared to placebo did not reduce the

number of births occurring before 37 weeks, as had happen before with other tocolytic drugs.

2. A secondary analysis showed that atosiban was more effective than placebo in delaying delivery for 24 hours, 48 hours and 7 days in those pregnancies of more than 28 weeks.
3. Perinatal mortality was higher in the atosiban group compared to placebo. However, the proportion of less than 28 weeks pregnancies was significantly greater in the atosiban group.
4. When used as maintenance therapy, atosiban delayed the first recurrence longer than placebo, but the perinatal results did not improve, nor did the necessity of intravenous tocolytic treatment.
5. Atosiban did not reduce the frequency of deliveries before 37 weeks or the neonatal morbidity or mortality when compared to ritodrine. However, its use resulted in a greater number of women that did not give birth and did not require an alternative tocolytic after seven days of treatment. At the same time side effects of the drug were less frequent when atosiban was used.
6. When comparing atosiban with terbutaline there were no differences in the time elapsed to delivery or in the use of rescue tocolytics. However, the mothers presented more secondary effects when treated with terbutaline.

DISCUSSION

Atosiban is comparable to β -agonists in delaying labor for up to 7 days, without being able of significantly prolong pregnancy or reduce perinatal morbidity and mortality. The drug is better tolerated than β -agonists, especially regarding cardiovascular symptoms that lead to discontinuing the β -agonist in many patients. The increase in perinatal mortality observed with atosiban may be due to the imbalance in the randomization of the extreme premature in the study that compares atosiban with a placebo and to the imbalance of the multiple pregnancies in the study that compares atosiban with ritodrine. However, it is not possible to be sure that this worst perinatal outcome is not a consequence of the drug or any other factor that has not been considered.

We estimate necessary to conduct new studies considering the variables that were not included in the randomization on

the mentioned studies (stratification by gestational age and number of fetuses). This will allow obtaining solid conclusions about the potential adverse effects of the drug to the newborn. We also estimate that the information is still not enough regarding the safety of the drug to the fetus and newborn, especially considering the lack of long term follow up.

We conclude that the available evidence does not justify the use of atosiban as the first line drug for treating premature labor. However, and given the fact that it is well tolerated; it constitutes a second line alternative in patients with premature labor that develop adverse effects with the first line drug. It is also a second line alternative for patients in whom the first line drug fails to succeed or for patients in which the use of β -agonists is contraindicated.

As we mentioned previously, atosiban and other tocolytics have been evaluated for their capacity of stopping premature labor in groups of patients that probably are not homogeneous. This means that we are handling in the same way and with the same drug, patients whose premature labor is probably caused by different etiologies.

We estimate that the appropriate management of premature labor requires an etiologic diagnostic of the condition, although we recognize that we are far from achieving that goal. If we, as an example, demonstrate that there is a subgroup of patients who's premature labor is caused by an increase in the biologic action of oxytocin, they will very likely have a more appropriate therapeutic response to atosiban compared to β -agonists. Having recently studied the phenomenon of premature labor associated with intrahepatic cholestasis of pregnancy, we have evidenced a greater sensibility of the myometrium to oxytocin in these patients, related to an increase in the expression of the myometrial oxytocin receptor induced by biliary acids (this study has been sent for publication).

We postulate that in this subgroup of patients, treatment of premature labor with an antagonist of the oxytocin receptor, like atosiban, would be a more logical strategy and potentially more efficient than the use of a routine tocolytic. Premature labor continues to be the greatest problem of modern obstetrics. We estimate that the etiologic diagnostic of this condition, associated with the use of specific drugs like the one described, represents an alternative with potentially greater benefit than the actual treatment.

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