REVIEW ARTICLE

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Atosiban for Preterm Labour

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Contents

Abstract

Oxytocin antagonists are synthetic analogues that have the nonapeptide structure of oxytocin. They act by competing with oxytocin for receptors in the myometrium. Animal experiments and pilot clinical studies have examined several agents and, of these, atosiban has been the object of extensive clinical trials. In a large placebo-controlled trial with >500 patients, atosiban reduced the number of premature deliveries over 7 days compared with placebo with no more adverse effects than placebo. In large multicentre studies comparing atosiban with β-adrenoceptor agonists, the efficacy of the two medications was similar for pregnancy prolongation for 48 hours and for 7 days. The adverse effects, particularly cardiovascular, were considerably more frequent in the patients receiving β-adrenoceptor agonists, who had to stop treatment significantly more often than the atosiban recipients. No fetal adverse effects were seen with atosiban and, in particular, no effect on baseline fetal heart rate, unlike with the β-adrenoceptor agonists. Neonatal outcome did not differ significantly according to the treatment. The usefulness of maintenance treatment after the initial 48 hours has not been confirmed.

Thus, the effectiveness of oxytocin antagonists appears to be similar to β-adrenoceptor agonists and the former are not accompanied by measurable adverse effects. Oxytocin antagonists were designed specifically as tocolytics and have been validated by the European Drug Agency. They may be the treatment of

choice for preterm labour, particularly in patients at risk of cardiovascular complications (e.g. multiple pregnancy, heart disease, etc.).

Prematurity remains the leading cause of neonatal morbidity and mortality.[1,2] Nonetheless, recent changes in practice mainly involve interventions to limit the consequences of preterm birth rather than prevent it. At the same time, paediatric management continues to improve.

It is clear that tocolysis alone cannot solve the problems of prematurity, for many reasons. First, infection, one of the most important of the known causes of preterm delivery,[3,4] often makes tocolysis illusive or even contrary to the best interests of the fetus. Secondly, the clinical prognostic criteria for the risk of preterm delivery (evaluation of uterine contractions and cervical modifications) are imperfect[1] and tocolysis is used, most often excessively.[5] Finally, β-adrenoceptor agonists (or β-mimetics), considered for a long time as the reference drugs for tocolysis, are accompanied by frequent and serious adverse effects, including pulmonary oedema, cardiac rhythm disorders and even death.[6,7]

Nonetheless, tocolysis has an important place in the management of threatened preterm delivery, especially because a prolongation – even a brief one – of pregnancy can allow the administration of corticosteroids and the organisation of *in utero* transfer. Furthermore, in the case of very preterm birth, the newborn is at extreme risk because of immaturity of different organs and intraventricular haemorrhage, and postponement of delivery by just a few days may be life saving.[8] Accordingly, obstetrical practitioners seek tocolytics that, for equal efficacy, have fewer adverse effects and serious complications than β-adrenoceptor agonists. Oxytocin antagonists and calcium channel antagonists appear to meet these requirements.

The aim of this article is to provide the reader with physiological and pharmacological data and clinical studies about atosiban, the main oxytocin antagonist currently used to treat preterm labour.

A literature search on Medline was conducted for the years 1960 to November 2003 with regard to oxytocin antagonists and atosiban. The keywords used were 'atosiban', 'oxytocin antagonist' and 'tocolytic'. The reference lists of identified articles were also examined manually to find additional relevant studies.

1. Pathophysiology of Preterm Labour

Oxytocin and arginine vasopressin (AVP) are two nonapeptides secreted by the posterior pituitary gland; they differ by only two amino acids.[9] Oxytocin secretion by the pituitary is pulsatile. Oxytocin is also produced by the myometrium, the placenta, the ovaries and the fetal membranes.[10]

Oxytocin has long been ascribed an important role in the initiation of preterm and term labour. Although preterm labour may be regarded as a syndrome with various aetiologies, oxytocin action on the uterus is probably to a large extent a common step in activation of the myometrium. Among the several pathophysiological processes ongoing with initiation of preterm parturition, there is an earlier increase in the concentration of oxytocin receptors in the myometrium as observed in term parturition.[11] However, it is not clear if increased release of oxytocin into the bloodstream, up-regulation of uterine receptors for oxytocin or locally released oxytocin is the major mechanism.[12-14] Vasopressin acting on uterine vasopressin V_{1A} receptors may also be involved, although this has been less studied.[15] Ethanol (alcohol) used several years ago for tocolysis was thought to mediate its effect by inhibiting endogenous oxytocin and AVP secretion by the neurohypophysis.[9] Oxytocin acts on the genesis of uterine contractions through two separate pathways. First, by binding to its receptors on the smooth muscle cell membranes, it increases the intracellular concentration of Ca^{2+} through the inositol triphosphate (IP3) pathway (and probably via the activation of calcium channels).[9] Secondly, it induces pros-

taglandin (PG) secretion in the decidua and fetal membranes via the diacylglycerol pathway. A paracrine effect causes these prostaglandins to act on the myometrial smooth muscle cells and activate uterine contractility. Prostaglandins also increase the concentration of oxytocin receptors in these cells.[9]

Because these reports show the involvement of oxytocin in the initiation of preterm labour, substantial efforts have been devoted to the development of oxytocin antagonists for tocolytic purposes in recent years.

2. Pharmacology

Atosiban, 1-(3-mercaptopropanoic acid)-2-(O-ethylD-thyrosine)-4-threonine-8-L-ornithine-oxytocin, is a synthesised cyclic nonapeptide that behaves as a competitive antagonist for oxytocin receptors.[16] The oxytocin molecule has been modified in positions 1, 2, 4 and 8, and can thus inhibit the uterotonic action of oxytocin completely, competitively and dose dependently.[17]

In vitro studies show that atosiban inhibits the oxytocin-induced increases of IP3 and intracellular Ca^{2+}, and reduces myometrial contractility.[15] Oxytocin antagonists have been shown to inhibit the *in vivo* oxytocin-induced production of $PGF_{2\alpha}$ in sheep.[18] On the other hand, they do not affect the release of PGE_2; this is important since PGE_2 maintains the permeability of the fetal ductus arteriosus.[9,19]

2.1 Pharmacokinetics

The pharmacokinetics of atosiban have been studied in healthy nonpregnant volunteers and in pregnant women. In a study of 11 nonpregnant women, Lundin et al.[20] described pharmacokinetics after administration of a bolus of 10 nmol/kg. Clearance was 0.623 ± 0.099 L/h • kg (standard error of the mean [SEM]) and the half-life was 16.2 ± 2.4 minutes (SEM). Peak plasma concentrations appeared 2–8 minutes after intravenous administration. Neither haemodynamic modifications nor other side effects were noted. Other studies[21,22] have reported bioavailability of 97% as well as binding to serum proteins (33%) and erythrocytes (13%). The volume of distribution in nonpregnant women was 13.1L ± 3.8 (mean ± SD).

Goodwin et al.[23] studied the pharmacokinetics of atosiban in eight pregnant women with preterm uterine contractions. Atosiban was administered by continuous intravenous infusion at a rate of 300 μg/minute until uterine contractions stopped for 6 hours or up to a maximum infusion length of 12 hours. Plasma atosiban concentrations reached steady state (442 ± 73 μg/L [mean ± SD]) within 1 hour. After completion of the infusion, plasma atosiban concentrations declined rapidly and biexponentially (initial half-life 13 ± 3 minutes; terminal half-life 102 ± 18 minutes). The effective half-life was 18 ± 3 minutes. Clearance was 41.8 ± 8.2 L/h and volume of distribution 18.3 ± 6.8.

Valenzuela et al.[24] have assessed the placental transfer of atosiban in eight women undergoing elective Caesarean section. Atosiban was infused at a rate of 300 μg/min until the umbilical cord was clamped. The study showed that very little atosiban crosses the placenta. The average ratio (± SD) for the fetal versus maternal concentration for atosiban was 0.124 ± 0.025. Drug concentrations in fetal circulation did not increase with longer infusion rates, suggesting that the drug does not accumulate in the fetus.

3. Clinical Trials

3.1 Preliminary Studies

Inhibition of uterine contractions with atosiban was first demonstrated in nonpregnant women.[25] Bolus administration of atosiban 0.2–1.25mg diminished the tonus and frequency of the uterine contractions induced by vasopressin. The first published reports of oxytocin antagonists for tocolysis came from Scandinavian studies at the end of the 1980s: the first publication[26] concerned a pilot study of 13 patients hospitalised for threatened preterm delivery between 28 and 36 weeks' gestation. After 2 hours of rest the patients received intravenous atosiban 10–100 μg/min for 1–10 hours. The frequency of contractions diminished in each patient and uterine

contractions stopped in eight. The tocolytic effect was dose dependent. There were no maternal or fetal adverse effects.

The second study used the same protocol and included 12 patients at 27–33 weeks' gestation.[27] Contractions stopped in nine patients. The three patients who did not respond to treatment were at <28 weeks' gestation; the nonresponse may thus be related to the low concentration of oxytocin receptors at so early a term.[9]

Therefore, these two Scandinavian studies found that atosiban was associated with a tocolytic effect in 86% of patients and that it may not be efficacious before 28 weeks gestation. Because they were not comparative studies, clinical trials comparing atosiban with a placebo were necessary.

3.2 Clinical Evaluation of Atosiban

The efficacy of oxytocin antagonists has been compared with that of placebo and β-adrenoceptor agonists.

3.2.1 Atosiban versus Placebo

In 1994, Goodwin et al.[19] published the results of a randomised trial intended to test the tocolytic efficacy of atosiban compared with placebo. The patients were all at 20–36 weeks' gestation upon entry. Atosiban 300 μg/min or placebo was administered by continuous intravenous infusion for a maximum of 12 hours. Of the 112 patients randomised in this trial, 56 were allocated to the atosiban group and 56 to the placebo group. The number of uterine contractions diminished significantly in the atosiban group compared with the placebo group (percentage decrease in contraction frequency was 55.3 ± 36.3 [mean ± SD] in the atosiban group versus 26.7 ± 40.4 in the placebo group, $p = 0.004$). Complete cessation of contractions was experienced by 25% (n = 14) of patients in the atosiban group and 5% (n = 3) of placebo recipients ($p = 0.007$). Prolongation of pregnancy did not differ significantly. Estimated gestational age at delivery was similar in both groups (37.8 ± 3.5 vs 38.3 ± 2.1 weeks [mean ± SD]). On the other hand, two children with patent ductus arteriosus and two with acute respiratory distress syndrome were reported in the atosiban group, and there were no reports of these complications in the placebo group. The authors prudently concluded only that atosiban inhibits uterine contractions and that oxytocin appears to play a role in the maintenance of uterine activity.

The second randomised, placebo-controlled atosiban trial was published in 2000 by Romero et al.[28] Their aim was to assess the efficacy and safety of tocolytic treatment with atosiban. This trial included 501 patients, 246 in the atosiban group and 255 in the placebo group. The initial treatment consisted of intravenous atosiban or placebo for 1 hour. Short-term intravenous therapy began with a bolus of atosiban 6.75mg. This was followed by an infusion of 300 μg/min of atosiban for 3 hours, then 100 μg/min of atosiban for up to 45 hours. A maintenance treatment was then begun (subcutaneous infusion of atosiban 30 μg/min) and continued until 36 weeks' gestation. However, the results of this study must be interpreted cautiously, especially in view of two particularities. First, if the treatment did not work within 1 hour, the physicians were authorised to prescribe another tocolytic agent ('rescue therapy'). Overall, 42% of the patients in the atosiban group and 51% of the patients in the placebo group did not respond to treatment and received second-line tocolytic treatment. Secondly, the randomisation did not result in the selection of comparable groups: the mean gestational age on admission in the atosiban group was significantly lower than in the placebo group (30.3 vs 31.0 weeks, respectively; $p = 0.008$), and the percentage of patients included before 26 weeks' gestation was also higher in the atosiban group (10% vs 5%).

The proportion of patients who remained undelivered and did not receive an alternate tocolytic at 24 hours (73% vs 58%, $p < 0.001$), 48 hours (67% vs 56%, $p = 0.008$) and 7 days (62% vs 49%, $p = 0.003$) was significantly greater in the atosiban than in the placebo group. This difference was especially clear for the patients included at 28 weeks' gestation or more. However, the neonatal results were less positive: perinatal mortality in the atosiban group (13 of 288 [4.5%]) was higher than in the placebo group (5 of 295 [1.7%]; $p < 0.05$). The authors explained this

Table I. Results of multicentre, randomised trials comparing atosiban with β-adrenoceptor agonists for tocolysis

Study details and	European Atosiban Study[30]		Canadian/Israeli Atosiban Study[29]		French/Australian Atosiban Study[31]	
outcome	atosiban	terbutaline	atosiban	ritodrine	atosiban	salbutamol
No. patients	116	129	128	124	119	122
Treatment duration (h)	18	13–18	18	18	18–48	48
Drug administration protocol	6.75mg bolus IV, 300 μg/min for 3h, 100 μg/min for 15h	5–20 μg/min	6.75mg bolus IV, 300 μg/min for 3h, 100 μg/min for 15h	0.10–0.35 mg/min	6.75mg bolus IV, 300 μg/min for 3h, 100 μg/min for 15–45h	2.5–45 μg/min
Prolongation of pregnancy >48h (%)	86.1	85.3	84.9	86.9	93.3	95
Prolongation of pregnancy >7d (%)	75.6	67.4	73	76	89.9	90.1
Gestational age at delivery (wks)	35.8	35.2	35.1	35.2	36.5	36.3
Maternal adverse effects (%)	4.3	75.2[a]	4.0	84.3[a]	16	80.3[a]
Discontinuation of treatment because of adverse effects (%)	1.7	13.2[a]	0.8	29.8[a]	0.8	10.7[a]
Perinatal mortality (no.)	3	7	2	1	1	4
NICU admission (%)	28	33	20.5	16.3	20.9	20.3

a $p < 0.05$ compared with atosiban group.

IV = intravenous; **NICU** = neonatal intensive care unit.

difference by the lower term of inclusion in the atosiban group and, in particular, by the higher percentage of patients included before 26 weeks' gestation in the group in which most of the perinatal deaths occurred. All deaths appeared to be associated with extreme prematurity.

This trial showed that atosiban has a place as a new tocolytic, since more pregnancies in the atosiban group were still ongoing after 7 days than in the placebo group. The differences in perinatal morbidity are probably due to the unbalanced selection produced by this particular randomisation. In more recent trials, perinatal mortality has not been higher in the patients receiving atosiban.

3.2.2 Atosiban versus β-Adrenoceptor Agonists

Three large, randomised trials[29-31] comparing atosiban with β-adrenoceptor agonists for tocolysis have recently been published. These trials included 245 patients in the European Atosiban Study Group,[30] 252 in the Canadian and Israeli Atosiban Study Group[29] and 241 in the French/Australian Atosiban Investigators Group[31] (table I presents their data). In summary, they show no significant difference between the two agents compared for prolongation of gestation or neonatal indicators. However, the oxytocin antagonists were associated with significantly fewer maternal adverse effects.

Data from the three randomised, controlled trials were pooled and published as the Worldwide Atosiban versus Beta-agonists Study Group. This international study[32] distinguished between tocolytic effectiveness, defined by the percentage of patients who did not give birth within 7 days after the initiation of the treatment, and treatment efficacy, defined as the percentage of women who did not give birth within 7 days and did not require alternative tocolytic treatment. Tocolytic effectiveness was similar for the two groups, but treatment efficacy at 7 days was greater with atosiban than β-adrenoceptor agonists (62% vs 49%, respectively; odds ratio 1.70 [95% CI: 1.17–2.46]). The patients in this study were enrolled at between 23 and 33 completed weeks' gestation. Mean gestation age at delivery was comparable in the two treatment groups (35.8 weeks for atosiban vs 35.5 weeks for β-adrenoceptor agonists, $p > 0.05$). The treatment

groups were comparable with regard to neonatal morbidity: for atosiban versus β-adrenoceptor agonists, respectively, admission to neonatal intensive care unit (31.4% vs 29.8%, $p > 0.05$), respiratory distress syndrome (19.5% vs 19.7%, $p > 0.05$) and cerebral haemorrhage (4.4% vs 5.3%, $p > 0.05$). The perinatal mortality rate was 14.7 per 1000 in the atosiban group and 27.7 per 1000 in the β-adrenoceptor agonists group, but the difference was not significant ($p = 0.19$). Neonatal deaths were related to prematurity. The results were stratified according to gestational age at inclusion (more or less than 28 weeks). The authors did not report excess of perinatal mortality in the atosiban group before 28 weeks, although this was not clearly stated in the manuscript. Treatment was stopped because of adverse effects ten times more often with the β-adrenoceptor agonists than with atosiban (81.2% vs 8.3%, $p < 0.05$). The β-adrenoceptor agonists also caused serious cardiovascular complications, including acute pulmonary oedema in two patients and myocardial ischaemia in one patient. Acute pulmonary oedema was also reported in a third patient who was initially included in the atosiban group but the complication occurred while she was receiving a β-adrenoceptor agonist.

3.2.3 Maintenance Treatment of Preterm Labour

Atosiban has also been evaluated for maintenance treatment of preterm labour in a randomised controlled trial.[33] In this study, atosiban was compared with placebo. The pregnancies included in the trial were not part of any other study of atosiban. Early intravenous therapy began with a bolus of atosiban 6.75mg administered for 1 minute. This was followed by an infusion of 300 μg/min for 3 hours and then 100 μg/min for <45 hours. Responders (patients who achieved uterine quiescence with atosiban) were subsequently randomly selected to receive subcutaneous maintenance therapy with either atosiban or matching placebo until 36 weeks' gestation. This may have constituted a bias of selection since patients enrolled in the study were preselected as responding to atosiban. This study included 251 patients in the atosiban group and 261 patients in the placebo group.

The time from the start of maintenance therapy to the first recurrence of labour was significantly longer in the atosiban group than in the placebo group (median number of days: 32.6 vs 27.6, $p = 0.02$). Deliveries before 32 weeks' gestation were comparable in the two groups, with values of 12% in the atosiban group and 14% in the placebo group ($p > 0.05$). Similarly, the preterm delivery rate was comparable between both groups (deliveries before 37 weeks of gestation: 34% in the atosiban group vs 38% in the placebo group, $p > 0.05$). Perinatal morbidity and mortality were similar in both groups. Adverse effects such subcutaneous injection site reactions were more common in the atosiban group (70% vs 48%, $p < 0.0001$) and frequently resulted in discontinuation of therapy (80% in the atosiban group vs 35% in the placebo group, $p < 0.001$). Therefore, maintenance tocolytic therapy with atosiban after successful treatment of an acute episode of preterm labour does not reduce the incidence of deliveries before 32 or 37 weeks' gestation, does not improve perinatal outcome and is associated with injection site reactions. Accordingly, the results of this study do not support the use of atosiban for maintenance tocolytic therapy.

3.2.4 Atosiban versus Other Tocolytic Agents

Unfortunately, atosiban has only been compared with placebo or β-adrenoceptor agonists.

Recent meta-analyses suggest that calcium channel antagonists are more effective and much better tolerated than β-adrenoceptor agonists.[6,34,35] Moreover, nifedipine seems to be associated with a lower occurrence of neonatal morbidity than β-adrenoceptor agonists.[7] Therefore, new randomised trials comparing atosiban with nifedipine are needed to establish their relative efficacy.

Recently, an *in vitro* study has shown that a combination of ritodrine plus atosiban exhibits a synergistic inhibition for myometrial activity, thus allowing the use of lower concentrations of each drug to achieve the same effect compared with each drug used alone. The potential for decreasing adverse effects and increasing efficacy when using a combination in clinical practice needs to be evaluated in clinical studies.[36]

Other tocolytic agents are not discussed in this review. Some may be effective but are associated with potentially severe adverse effects (i.e. NSAIDs[37,38]). For others, there is no evidence that they are able to prevent preterm labour (i.e. magnesium sulfate[39-42]).

4. Dosage and Administration

The recommended protocol according to the European Drug Administration registration is as follows.[32]

Atosiban (Antocin®[1], Ferring Pharmaceuticals©, Malmo, Sweden):

- intravenous administration;
- 6.75mg bolus, direct intravenous, in 0.9mL saline;
- then 300 μg/min in a 5% glucose solution for 3 hours followed by 100 μg/min for 15–45 hours; and
- no maintenance treatment.

5. Conclusions

Numerous studies have demonstrated the efficacy of atosiban as a tocolytic in animals and in humans, although the first report raised concerns about its effects on neonatal safety (mortality). These adverse effects were probably the result of unbalanced selection in the randomisation and these concerns have been alleviated by recent multicentre studies. Of the new tocolytics registered at the present time, atosiban has undergone the most thorough pharmacological and methodological evaluation. It can be used as a first-line treatment for treatment of acute preterm labour. New clinical studies are needed to compare its efficacy with that of calcium channel antagonists, which also appear to present advantages in comparison with β-adrenoceptor agonists. Finally, newly synthesised agents behaving like selective oxytocin antagonists and not affecting AVP are currently under evaluation and may be useful in clinical practice.

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