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ORIGINAL ARTICLE

The oxytocin antagonist atosiban *versus* the β-agonist terbutaline in the treatment of preterm labor

A randomized, double-blind, controlled study

THE EUROPEAN ATOSIBAN STUDY GROUP

A complete list of the members of the European Atosiban Study Group and their respective academic institutions appears at the end of the article

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Objective. To compare the efficacy and safety of atosiban and terbutaline for the inhibition of preterm labor.
Methods. Two hundred and forty-nine women diagnosed with preterm labor at 23–33 weeks of gestation were enrolled of whom 245 women received treatment, 116 with atosiban and 129 with terbutaline. At randomization, women were stratified by gestational age (≤28 weeks and >28 weeks). Atosiban (iv bolus dose of 6.75 mg, then 300 μg/min for 3 h and 100 μg/min thereafter) and terbutaline (5–20 μg/min) were administered by iv infusion for 13–18 h. Re-treatment with study drug or an alternative tocolytic agent was allowed. Tocolytic effectiveness was assessed in terms of the number of women undelivered after 48 hours and 7 days and efficacy and tolerability in terms of the number of women remaining undelivered and not requiring alternative tocolytic therapy after 48 hours and 7 days of starting therapy. Safety was assessed in terms of maternal side effects and neonatal morbidity.
Results. Tocolytic effectiveness at 48 hours was 86.1% *vs* 85.3%; $p=0.783$, and after 7 days it was 76.5% *vs* 67.4%; $p=0.067$, in the atosiban and terbutaline groups, respectively. Tocolytic efficacy and tolerability after 48 hours was 72.2% *vs* 68.2%; $p=0.51$ and after 7 days was 55.6% *vs* 43.4%; $p=0.08$ in the atosiban and terbutaline groups, respectively. Overall, there were fewer clinically important adverse events with atosiban than with terbutaline.
Conclusions. The efficacy of atosiban in the inhibition of preterm labor was shown to be comparable to terbutaline. Atosiban had a superior safety profile compared with terbutaline in terms of maternal and fetal adverse events, and comparable infant outcomes.

Key words: atosiban; oxytocin antagonists; preterm labor; terbutaline; β-agonist

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Preterm birth accounts for 69–83% of all neonatal deaths among normally formed infants (1, 2). The majority of preterm births are preceded by the onset of premature and untimely uterine contractility (preterm labor) in pregnancies not associated with preterm prelabor rupture of the membranes.

Abbreviations:
APT: all patients treated; bpm: beats per minute; CNS: central nervous system; NICU: neonatal intensive care unit.

The most commonly used treatment of spontaneous preterm labor is the pharmacological inhibition of preterm uterine contractions with β-adrenergic agonists (β-agonists; e.g. fenoterol, ritodrine, salbutamol and terbutaline). These agents have been shown to be effective in reducing the incidence of delivery within 24 h and 48 h of treatment (3, 4), but do not appear to decrease the likelihood of preterm delivery or perinatal mortality, or reduce the number of infants being born with a low

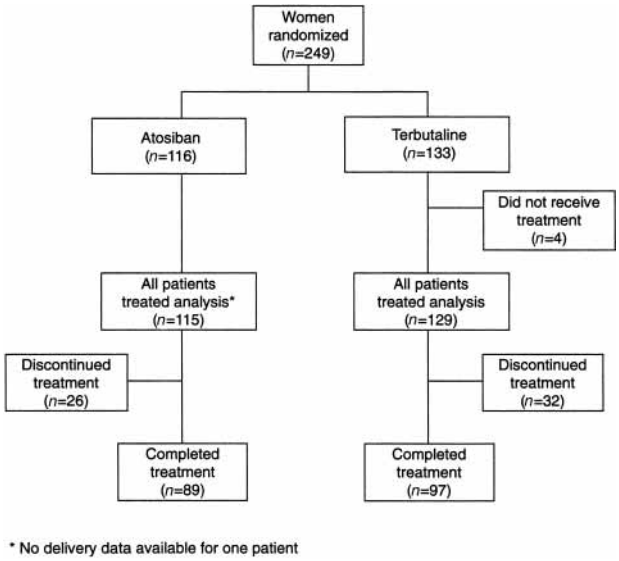

Fig. 1. Study population: flow of women through the study.

birth weight (i.e. <2500 g) (4, 5). In addition, the low uterine specificity of β-agonists is associated with unwanted and potentially hazardous adverse events such as maternal myocardial ischemia (6), maternal pulmonary edema (7) and maternal death (8). Consequently, other pharmacological agents have been investigated, including oxytocin receptor antagonists (9).

Atosiban ([1-deamino-2-D-Tyr(OEt)-4-Thr-8-Orn]-oxytocin) is a competitive oxytocin receptor antagonist developed for the treatment of preterm labor (10). Specific inhibitors of oxytocin-induced uterine contractility, such as atosiban, have been developed on the premise that increased oxytocin receptor density in the myometrium during pregnancy correlates directly with increased uterine activity (11). Pre-clinical studies have shown that atosiban inhibits uterine contractions mediated by oxytocin in both *in vitro* and *in vivo* animal models (10). More recently, Phase I and II clinical studies in healthy volunteers and pregnant women have shown good tolerability to atosiban (12), with no significant cardiovascular, pulmonary or CNS side effects (13), and atosiban has been shown to be effective in diminishing or stopping uterine contractions in women with threatened preterm birth (13, 14).

This Phase III clinical trial was part of an international program aimed at comparing the safety and efficacy of atosiban with different β-agonists for the treatment of preterm labor. This study, carried out in the Czech Republic, Denmark, Sweden and the UK, was designed to compare the safety and efficacy of atosiban with terbutaline, a β-agonist used in routine clinical practice.

Methods

This multicenter, double-blind, double-placebo, randomized, controlled trial was conducted at 31 sites in the Czech Republic (9), Denmark (2), Sweden (8) and the UK (12). Two hundred and forty-nine women diagnosed with preterm labor between 23 and 33 weeks of gestation were enrolled during the study period (March 1994 to December 1996) and randomized to either atosiban (n=116) or terbutaline (n=133) (Fig. 1). The definition of preterm labor and the eligibility criteria for study entry are shown in Table I.

The study was approved by all of the relevant ethics committees and was conducted in accordance with the ethical principles contained in the Declaration of Helsinki. Signed, informed consent was obtained from every woman enrolled. Computer-generated randomization lists for each center were used to allocate women to study treatment

Table I. Eligibility criteria for study entry

Inclusion criteria
Preterm labor, as defined by:
Uterine contractions: the presence of regular contractions of ≥30 s duration, at a rate of ≥4/30 min confirmed by external tocography
Cervical dilation and effacement: 0–3 cm (nulliparas) or 1–3 cm (primiparas or multiparas) and ≥50%, respectively
≥18 years of age
Gestational age: between 23 and 33 completed weeks confirmed by ultrasound performed before 20 weeks, and/or reliable menstrual dates
Previous tocolytic therapy: termination of any other on-going tocolytic therapy (UK and Czech Republic only)
Exclusion criteria
High order multiple pregnancy
Ruptured amniotic membranes
Major vaginal bleeding
Use of non-steroidal anti-inflammatory agents for tocolysis within previous 12 h
Severe pre-eclampsia*/hypertension†
Body temperature >37.5°C (in the UK and Czech Republic) or >38°C (in Sweden and Denmark)
Urinary tract infection
Fetal/placental/uterine abnormalities:
Suspected chorioamnionitis, abruptio placentae, placenta previa, intrauterine growth retardation, fetal distress/death, major congenital anomaly, hydramnios, retained intrauterine device
Serious maternal disease:
Cardiovascular disease, symptomatic hyperthyroidism, uncontrolled diabetes mellitus, pheochromocytoma, asthma
Any contraindication to the use of terbutaline
Alcohol or drug abuse
History of hypersensitivity to any of the components of the study drugs
Participation in a clinical trial of an experimental drug within the previous month

* Defined as diastolic blood pressure >110 mmHg and/or >0.3 g albumin in a urine sample in Sweden and Denmark.

† Defined as requiring medication in the UK and Czech Republic, and systolic blood pressure >150 mmHg and/or diastolic blood pressure >110 mmHg in Sweden and Denmark.

and women were stratified by gestational age ≤28 weeks and >28 weeks at enrolment. Stratification ensured that the two treatments were equally distributed over both strata of the study.

After randomization and allocation to treatment group, women were administered atosiban or terbutaline as follows:

- Atosiban (Tractocile®, Ferring AB, Malmö, Sweden) was given as a single iv bolus dose (6.75 mg in 0.9 ml normal saline), followed by an iv infusion of 300 μg/min atosiban in 5% dextrose for the first 3 h and then 100 μg/min atosiban in 5% dextrose for up to 18 h. Separately but simultaneously, a placebo iv infusion of 5% dextrose corresponding to terbutaline was administered as per the product labelling. Both iv infusions were given for the same period of time.
- For the terbutaline group, a placebo (0.9 ml normal saline) was administered as a single bolus injection followed by an iv infusion of 5% dextrose at a rate corresponding to the atosiban infusion (see above). Separately but simultaneously, terbutaline (Bricanyl®; Astra Draco, Lund, Sweden) was given as an iv infusion in 5% dextrose at 10–25 μg/min. Both infusions ran for up to 18 h.

Prior therapy at inclusion was permitted during the study. Such extra therapy was recorded, including the use of any tocolytic agent in the 6-h period prior to study enrolment in women transferred, use of corticosteroids, thyrotrophin-releasing hormone and antibiotics.

The primary and secondary efficacy/safety outcomes of the study were chosen based on the observations of The Canadian Preterm Labor Investigators Group (5). The main outcomes of interest in the All Patients Treated (APT) analysis population were the effectiveness and safety of atosiban *versus* terbutaline in conventional tocolytic therapy. Tocolytic effectiveness was assessed in terms of the total number of women undelivered after 48 hours and 7 days of starting treatment. Safety was assessed by maternal side effects, with particular emphasis on cardiovascular adverse events and neonatal morbidity. Tocolytic efficacy and tolerability was assessed in terms of the proportion of women who did not require alternative tocolysis within 48 hours and 7 days of initiation of therapy. The latter composite endpoint was used in this study since this accounts for treatment failure as a measure of either efficacy (ie. the need for an alternative tocolytic due to labor progression) or tolerability (ie. those women who discontinued treatment due to adverse events). Consequently, the efficacy endpoint used in this study was a composite of both efficacy and tolerability.

Secondary efficacy outcomes included the contraction rate with time, the mean gestational age at delivery, the proportion of women re-treated with study medication, the proportion of infants born at differing gestational ages, and the number of infants requiring neonatal intensive care.

Women who had a recurrence of preterm labor at any time after the cessation of study treatment could be re-treated with the same iv medication administered previously, provided that all previous treatments were successful and no alternative tocolytic therapy was given, gestational age was <34 weeks, and all other eligibility criteria were still met. Recurrence or progression of preterm labor was assumed when any two of the following three criteria were met: a contraction rate ≥4/h, an increase in cervical dilation of ≥1 cm from the initial measurement, and an increase in cervical effacement ≥25% from the initial measurement.

The administration of an alternative tocolytic agent was dependent on both efficacy and tolerability of study medication. An assessment of study treatments was optional at 6 or 12 h after initiation of therapy if the investigator was concerned that labor was progressing despite study drug administration. At the end of the infusion period, this assessment was compulsory.

Uterine contraction frequency was monitored continuously for the first 2 h after the initiation of treatment using an external tocodynamometer, and then for 60 min at 6 and 12 h and for 30 min at 24 and 48 h (UK, Czech Republic), or for 30 min or until 4 contractions had been detected at 6, 12, 24 and 48 h (Sweden and Denmark).

Maternal/fetal heart rate and maternal blood pressure were recorded at baseline (i.e. prior to study treatment) and then every 20 min for the first hour and then hourly until the infusions were completed. Routine laboratory parameters were recorded for all treated women at baseline and after completion or termination of study infusions.

Data from all 31 sites were entered into a central clinical trial database and after clarification checks, the database was transferred to the Biometrics Department, Ferring Pharmaceuticals, for statistical analysis.

The analysis population (APT) included all women who received any study medication. The first primary efficacy outcome, the proportion of women undelivered and not requiring alternative tocolysis within 7 days of treatment initiation, was analyzed using the Mantel-Haenszel test, which is a stratified test controlling for the center effect (15), and using the Kaplan-Meier method. The second primary efficacy outcome, gain in gestational age from enrolment to delivery or alternative tocolysis, was analyzed using the stratified log-rank test, which was stratified for center (16). Sec-

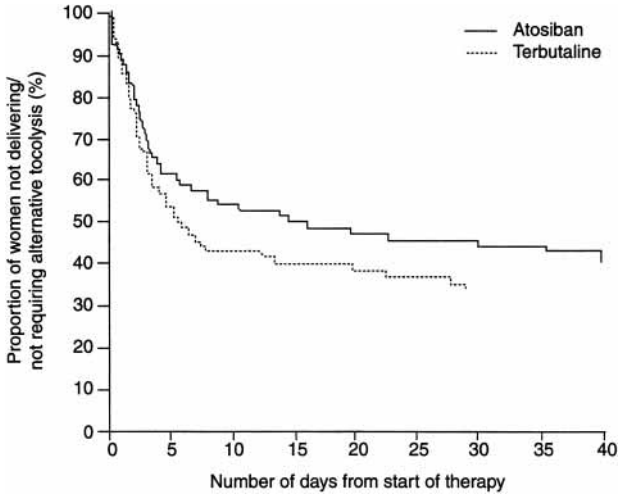

Fig. 2. Kaplan-Meier estimates for the number of days from start of therapy to either time of delivery or administration of alternative tocolysis for the atosiban and terbutaline treatment groups. From this survival curve, the primary endpoint (objective) efficacy and tolerability are derived.

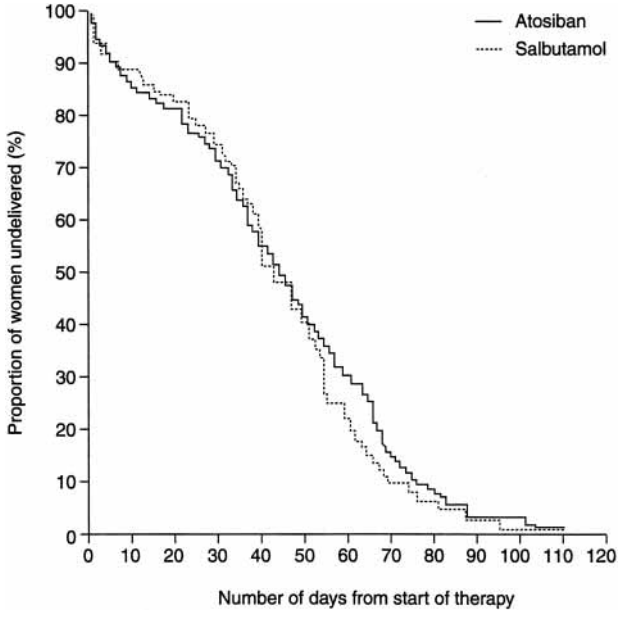

Fig. 3. Kaplan-Meier estimates for the number of days from start of therapy to time of delivery for the atosiban and terbutaline treatment groups. From this survival curve, the primary endpoint (objective) effectiveness can be derived.

ondary efficacy outcomes were analyzed using the Wilcoxon Rank sum test (normal approximation) or the Chi-square test, Fisher's exact test depending on whether the data were categorical or continuous. A sample size of 120 women per treatment group was calculated to achieve a power of 80% when using an upper significance value of 5% (type I error).

Results

Study population

Of the 249 women enrolled during the study period, four women were randomized to the terbutaline group but did not receive terbutaline treatment. The remaining 245 women received study treatment and were included in the APT population (Fig. 1). One woman in the atosiban group was subsequently lost to follow up (no delivery data available).

Both the atosiban and terbutaline treatment groups were comparable in terms of demographic and baseline characteristics (Table II), with the exception of a greater number of twin pregnancies in the terbutaline group with a gestational age ≤28 weeks. However, this was not statistically significant ($p=0.057$).

Tocolytic outcomes

The Kaplan-Meier curves (Fig. 2 and 3) were used to derive the two primary end points for atosiban and terbutaline.

Effectiveness

The number of women remaining undelivered after 48 hours was 86.1% ($n=99$) in the atosiban group and 85.3% ($n=110$) in the terbutaline group ($p=$

Table II. Demographic and baseline characteristics of the APT population

	Treatment group*	
	Atosiban ($n=116$)	Terbutaline ($n=129$)
Age, years (mean±s.d.)	27.3±5.8	26.4±5.7
Ethnic group (%)		
White	88.8	90.7
Black	4.3	3.1
Oriental	1.7	1.6
Other	5.2	4.6
Estimated gestational age, weeks (mean±s.d.)	30.0±2.3	29.8±2.6
Parity (%)		
0	49.1	52.6
≥1	50.9	47.3
Pregnancy status by gestational age group (%)		
Singletons		
≤28 weeks	15.7	16.3
>28 weeks	71.3	65.1
Twins		
≤28 weeks	2.6	8.5
>28 weeks	10.4	10.1
Median contraction frequency, no./ 30 min (range)	8 (4–48)	7 (4–22)
Median cervical dilation, cm (range)	1 (0–3)	1 (0–3)

*No parametric analysis available.

Table III. Pregnancy outcome data for the APT population

	Treatment group					
	Singletons			Twins		
	Atosiban[ψ]	Terbutaline	*p*	Atosiban	Terbutaline	*p*
No. of infants	100	105		30	48	
Estimated gestational age at delivery, weeks (mean±s.d.)	35.8±4.1	35.2±4.2	0.29	32.8±3.7	32.3±4.6	0.82
Birth weight, g (mean±s.d.)	2636±790	2495±893	0.21	1928±676	1868±901	0.63
Number of infants (%) born by gestational age at delivery (weeks)						
≤28 weeks	18 (18%)	21 (20%)		6 (20%)	22 (45.8%)	
>28 weeks	82 (82%)	84 (80%)		24 (80%)	26 (54.2%)	
Admission to neonatal intensive care unit*						
No. of infants *n* (%)	28 (28)	35 (33.3)		16 (53.3)	29 (60.4)	
No. of days (mean±s.d.)	15.8±16.0	17.2±18.5	0.91	20.5±22.5	22.3±36.9	0.25

*Includes infants from both atosiban-treated women and women administered atosiban and alternative tocolytic therapy.
[ψ]Data missing for one patient.

0.78). The number of women undelivered after 7 days of starting treatment was 76.5% (n=88) in the atosiban group and 67.4% (n=87) in the terbutaline group (p=0.07).

Efficacy and tolerability

The proportion of women undelivered and not requiring alternative tocolytic therapy within 48 h of treatment initiation was 72.2% (n=83) in the atosiban group and 68.2% (n=88) in the terbutaline group (p=0.52).

The proportion of women remaining undelivered and who did not require alternative tocolytic therapy within 7 days of treatment initiation was 55.6% (n=64) in the atosiban group and 43.4% (n=56) in the terbutaline group (p=0.08).

Secondary outcomes

A marked reduction in uterine contraction frequency was noted in both treatment groups after 20 min of starting treatment. From this time point onwards, smaller but similar decreases were observed in both treatment groups until 12 h post-treatment, when the mean contraction frequency was <2/h for both study treatments.

The gestational age at delivery (mean±s.d.) was not significantly different between either singleton (p=0.29) or twin (p=0.82) pregnancies of the atosiban and terbutaline groups (Table III). Birth weight also did not differ significantly between singletons of mothers administered atosiban and terbutaline (p=0.21), or between twins in the atosiban and terbutaline groups (p=0.63).

Maternal outcomes

The incidence of maternal adverse events for the safety population is shown in Table IV. Of great clinical importance were chest pain (0.9% atosiban, 2.3% terbutaline) and dyspnea (0% atosiban, 7.8% terbutaline). The other differences between treatment groups had a direct association with cardiovascular adverse events, principally tachycardia (4.3% atosiban, 75.2% terbutaline) and palpitations (0% atosiban, 9.3% terbutaline). Further adverse events of clinical interest, including vomiting, headache, tremor, hyperglycemia and hypoka-

Table IV. Maternal adverse events for the APT population stratified by primary treatment drug with or without alternative tocolytic therapy

	Number of adverse events (%) and received alternative tocolytic therapy (no/yes)*			
	Atosiban		Terbutaline	
Adverse event	No (n=77)	Yes (n=39)	No (n=73)	Yes (n=56)
Hypotension	4 (5.2)	1 (2.6)	3 (4.1)	2 (3.6)
Tachycardia	3 (3.9)	2 (5.1)	55 (75.3)	42 (75.0)
Palpitation	0	0	6 (8.2)	6 (10.7)
Syncope	0	0	0	1 (1.8)
Chest pain	1 (1.3)	0	2 (2.7)	1 (1.8)
Dyspnea	0	0	8 (11.0)	2 (3.6)
Hypokalemia	0	0	5 (6.9)	3 (5.4)
Hyperglycemia	8 (10.4)	3 (7.7)	16 (21.9)	14 (25.0)
Vomiting	2 (2.6)	1 (2.6)	10 (13.7)	11 (19.6)
Headache	2 (2.6)	3 (7.7)	12 (16.4)	10 (17.9)
Tremor	1 (1.3)	0	17 (23.3)	8 (14.3)
Anxiety	0	1 (2.6)	2 (2.7)	0
Nausea	10 (13.0)	6 (15.4)	12 (16.4)	7 (12.5)

*No parametric analysis available.

lemia (defined according to reference values of local laboratories), were also more frequently reported in terbutaline-treated women. Discontinuation of atosiban treatment due to maternal adverse events was reported in 1.7% ($n=2$) of women, while 13.2% ($n=17$) of women terminated terbutaline treatment prematurely because of adverse events.

Mean maternal heart rate (bpm) varied only slightly over the study period in women administered atosiban (min. 82.3, max. 85.9), whereas it increased markedly during terbutaline treatment (min. 88.1, max. 115.5). There were no clinically relevant differences between the two treatment groups in terms of maternal blood pressure (mmHg), neither regarding the mean maternal systolic (atosiban min. 62, max. 170; terbutaline min. 70, max. 177) nor diastolic blood pressures (atosiban min. 20, max. 112; terbutaline min. 35, max. 103).

Perinatal outcomes

Fetal outcomes

Fetal tachycardia, defined as a heart rate >170 bpm, associated with tocolytic treatment accounted for the large difference in reported fetal adverse events between treatment groups, with tachycardia occurring in 44.2% ($n=57$) of pregnancies in the terbutaline group and 6.0% ($n=7$) of pregnancies in the atosiban group. The incidence of fetal bradycardia (2.6% atosiban, 3.9% terbutaline), defined as a heart rate <100 bpm, was similar in both treatment groups.

Table V. Neonatal/infant morbidity of singletons and twins from the APT population stratified by primary treatment drug in singletons

	Number of adverse events (%)*			
	Singletons		Twins	
Adverse event	Atosiban $n=101$	Terbutaline $n=105$	Atosiban $n=30$	Terbutaline $n=48$
Hypoxia/asphyxia	1 (1.0)/0	0/1 (0.9)	0/0	0/0
Acidosis	2 (2.0)	1 (0.9)	0	7 (14.6)
Respiratory distress syndrome	17 (16.8)	28 (26.7)	10 (33.3)	19 (39.6)
Patent ductus arteriosus	6 (6.0)	4 (3.9)	2 (6.7)	10 (20.8)
Cerebral hemorrhage†	3 (3.0)	4 (3.9)	4 (13.3)	9 (18.8)
Hypotension	4 (4.0)	5 (4.9)	2 (6.7)	10 (20.8)
Sepsis	10 (10.0)	9 (8.9)	3 (10.0)	12 (25.0)
Apnea	4 (4.0)	2 (1.9)	0	1 (2.1)
Bradycardia	6 (6.0)	2 (1.9)	1 (3.3)	5 (10.4)
Hypoglycemia	4 (4.0)	5 (4.9)	4 (13.3)	9 (18.8)
Anemia	4 (4.0)	7 (6.9)	2 (6.7)	11 (22.9)
Thrombocytopenia	0	1 (0.9)	0	1 (2.1)
Arrhythmia	0	0	2 (6.7)	0
Retinal disorder	2 (2.0)	4 (3.9)	3 (10.0)	6 (12.5)

*No parametric analysis available.
†Includes intraventricular hemorrhage.

Neonatal/infant outcome

There were three neonatal/infant deaths in the atosiban group and seven neonatal/infant deaths in the terbutaline group, which were all considered by the investigator(s) to be unrelated or unlikely to be related to study treatment, but possibly related to infant prematurity. Eight of the ten deaths were in twin pregnancies (two atosiban and six terbutaline), with a gestational age at delivery between 24^{+0} and 27^{+0} weeks. The one singleton in the terbutaline group (delivered at 31^{+5} weeks of gestation) had a serious congenital anomaly (trisomy 18) and the other singleton was in the atosiban group and delivered at 33^{+4} gestational weeks.

The incidence of neonatal morbidity, excluding congenital anomalies, in infants born to women treated with atosiban or terbutaline is shown in Table V. Respiratory distress syndrome accounted for the majority of neonatal adverse events in both study groups (atosiban 20.6%, terbutaline 30.7%). Other adverse events of clinical interest, including sepsis, patent ductus arteriosus, hypoglycemia, hypotension and cerebral hemorrhage, were all less frequently reported in infants born to atosiban-treated women. It should be noted that adverse events, from a clinical trial perspective, were all events observed until discharge from hospital or neonatal death. None of the infant adverse events reported were considered to be related to the tocolytic study medication; most were attributed to the delivery process and prematurity. The incidence of congenital anomalies was similar in both treatment groups (atosiban 8%, terbutaline 6%).

Data on neonatal/infant outcomes were comparable in the atosiban and terbutaline groups. The proportion of neonates with 5-min Apgar scores of 0–3, 4–6 and 7–10 was 0% and 0.7%, 1.5% and 5.2%, and 96.9% and 91.5% for the atosiban and terbutaline groups, respectively. The mean number of days spent in an NICU did not differ between the atosiban and terbutaline groups for the infants from singleton pregnancies ($p=0.91$), or those from twin pregnancies ($p=0.25$) (Table III).

Discussion

The primary and secondary efficacy analyses of this study indicate that atosiban is comparable to terbutaline in the inhibition of preterm labor. However, atosiban was better tolerated by the mother and fetus than terbutaline, and neonatal/infant outcomes were comparable in both treatment groups. A dose-ranging study of atosiban

has shown that a dose comparable to the one administered in this study was similar in effectiveness to ritodrine (a β-agonist) in inhibiting uterine contractions in women in preterm labor and that these women reported fewer adverse events during study treatment (12). A more recent comparative trial between atosiban and ritodrine supports this observation. Only one woman discontinued treatment in the atosiban group 1/126 (0.8%) compared with 36/121 (29.8%) in the ritodrine group. No fetal or neonatal adverse events were reported and infant follow up did not show any longer term detrimental effects (17). In previous placebo-controlled studies, atosiban reduced uterine contractility in women to a significantly greater extent than placebo (13, 18) without causing significant cardiovascular, pulmonary or CNS side effects (13). Consequently, the results from this study confirm and extend the data from other randomized, controlled studies of atosiban.

Treatment discontinuation was greatest during the first episode of preterm labor in our study. Seventeen of 129 (13.2%) women experienced adverse events and stopped terbutaline treatment early, in contrast to a treatment discontinuation rate of only 1.7% (2/116) in atosiban-treated women. The adverse events which caused atosiban treatment to be discontinued prematurely were one case of rash and one case of headache. The difference in reported adverse events between study medications was mostly due to cardiovascular effects.

In terms of maternal adverse events, maternal tachycardia, palpitations, tremor and hyperglycemia following terbutaline administration were the most frequently reported but predictable adverse events, since they are all documented side effects of β-agonists (9, 19). Through the use of a double-blind, double-dummy technique, the utmost effort was made to keep the study blinded. At randomization until the start of treatment there was no study bias possible. However, it is feasible that the somewhat obvious side effect profile of terbutaline may have compromised the actual blinding during treatment.

Most fetal adverse events associated with terbutaline administration were similarly related to the non-specific pharmacological action of β-agonists, and their placental transfer and accumulation in fetal blood (20). Valenzuela and coworkers, in contrast, found only minimal transfer of atosiban from the maternal to the fetal circulation (21). Medically more serious maternal adverse events were chest pain and dyspnea, which were more frequently reported in terbutaline-treated women. Cardiac ischemia (6) and sudden maternal death (22) have been reported in women treated with ritodrine and terbutaline, respectively, although a study using low-dose terbutaline found fewer adverse cardiopulmonary effects associated with β-agonist administration than had previously been reported in the literature (23). In our study we found abnormally low concentrations of potassium in a number of terbutaline-treated women. Hypokalemia is another side effect attributed to β-agonist usage that can potentially lead to significant renal sodium and fluid retention, causing cardiac arrhythmias (24) and pulmonary edema (25) during tocolysis. Leveno and Cunningham (26) suggested that maternal pulmonary edema is a major complication of β-agonist administration, although their calculated incidence of pulmonary edema has been questioned (7). However, there are published case reports of pulmonary edema with the use of β-agonists in the literature (27–31) and it remains a potential complication in women when β-agonists are used inappropriately (7).

Neonatal/infant adverse events were comparable in the study groups. None of the neonatal or infant deaths were assumed to be related to study treatment but were possibly associated with infant prematurity, considering that eight out of the ten deaths occurred in twins at <28 weeks of gestation. The imbalance between the atosiban and terbutaline groups with regard to twins was possibly a result of the randomization process, because randomization was carried out per center rather than per country, which is an inherent problem of multicenter, and particularly multinational, trials. The disproportionate number of deaths in the terbutaline twin group was therefore attributed to high-risk pregnancies of low gestational age.

The tocolytic effectiveness was assessed in terms of the total number of women undelivered after 48 hours and 7 days of starting treatment. This was considered a valid endpoint for this study based on the results from previous studies of β-agonists and the administration of corticosteroid therapy. The Canadian Preterm Labor Investigators Group (5) reported a significant difference between ritodrine and placebo in delaying delivery for >24 h and >48 h ($p<0.001$), but as the 7-day endpoint was not a stated objective in their protocol, it was not considered relevant even though the difference in treatments at this time point was statistically significant. However, this efficacy endpoint was regarded as the most appropriate for our study since it is the maximum demonstrated β-agonist efficacy endpoint and may be of particular relevance for well tolerated tocolytic agents. In addition, the delay in delivery provided by tocolytic therapy is only of clinical benefit when the time gained is used effectively and consequently enables *in utero* transfer to a specialized care center (32) and/or the antepartum administration of corticosteroids (33, 34). The

greatest benefit for the neonate of corticosteroid therapy starts at 24 hours and lasts for up to 7 days after treatment *in utero* (35), the endpoint considered of value in this study.

Tocolysis is believed to be a short-term therapy for preterm pregnancies of low gestational age. This rather limited application is probably due to the considerable number of systemic adverse events associated with the non-specific tocolytic agents currently available, particularly the β-agonists. Terbutaline is one of the most widely used tocolytic drugs (36) but there is considerable variation in the efficacy, tolerability and administration of terbutaline reported in the literature (37–47). Although more acceptable methods of administering β-agonists are being developed, including iv terbutaline pumps for maintenance therapy (37, 47) and oral sustained-release ritodrine (48, 49), an inconvenient dose-titration regimen, as used in this study, is still the common practice and this will also contribute to restricting the use of tocolysis. The development of better tolerated and more efficacious, acceptable and convenient tocolytic agents may allow preterm pregnancies to be treated more effectively and safely and may widen their application to preterm pregnancies >32 weeks of gestation (34, 50, 51), the period in which the majority of preterm deliveries occur (52). In order to accomplish this objective, present difficulties in diagnosing preterm labor must be overcome, since many women are currently treated inappropriately and are being exposed to the potentially harmful effects of tocolytic drugs. Our study has shown that atosiban was comparable to terbutaline in inhibiting preterm labor in women between 23 and 33 weeks of gestation, without the inconvenience of dose titration. Atosiban was better tolerated by mother and fetus than terbutaline and infant outcomes were comparable. In conclusion, iv atosiban appears to be an effective and well tolerated treatment for women in preterm labor.

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