A Guide to the Cochrane Review of Oxytocin Receptor Antagonists

Oxytocin receptor antagonists for inhibiting preterm labour: a Cochrane systematic review.

Papatsonis D, Flenady V, Cite S and Liley H

Other publications by the lead author


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Interrogating the key findings

Efficacy versus placebo

These results are based on a single study that arguably should not have been included:
- sub-therapeutic doses of atosiban (TRACTOCILE) were given to women
- primary objective of the study was to evaluate the effect of atosiban on preterm uterine activity – ‘...efficacy conclusions are invalid.’

Infant outcomes versus placebo

Most of the outcomes conclusions are based on a single study with severe limitations:
- widely acknowledged imbalance in treatment groups, with more women at very low gestational ages and in more advanced preterm labour receiving atosiban
- despite this, most mortality parameters assessed were comparable with placebo
- the increase in infant mortality only differed significantly from placebo when data up to 12 months of age were included
- infant outcomes conclusions are invalid based on the available trial data; no atosiban trial has been designed to assess infant outcome.

Outcomes versus 3-agonists

The only study that significantly favours 3-agonists (birth weight < 1500 g) is not derived from the complete data set available:
- available data from two key trials are excluded
- most other endpoints favoured atosiban, including fetal, neonatal and perinatal death and maternal adverse drug reactions.

Critique of the main conclusions

Efficacy

'...atosiban was shown to have similar tocolytic efficacy to ...placebo.'

- efficacy data are taken from a single trial in which more women at extremely early gestational ages and more advanced labour (ie women at higher risk) received atosiban (P < 0.001)
- at the time of the trial, the investigators stated that this imbalance may have accounted for the increase in fetal-infant deaths
- subsequent trials have not demonstrated an increase in infant deaths.

Infant outcomes

'...atosiban was associated with more infant deaths...'

- these data are from a single trial in which more women at extremely early gestational ages and more advanced labour (ie women at higher risk) received atosiban (P < 0.001)
- the increase in infant mortality only differed significantly from placebo when data up to 12 months of age were included
- infant outcomes conclusions are invalid based on the available trial data; no atosiban trial has been designed to assess infant outcome.

Atosiban (TRACTOCILE) has comparable efficacy to 3-agonists at 48 hours, superior efficacy at 7 days and is associated with significantly fewer maternal adverse events

Infant deaths were associated with extreme prematurity, not study medication

The efficacy and safety of atosiban have been demonstrated in 742 women in randomised clinical trials and in a confirmed in European clinical practice study in more than 800 women

An expert’s view – ‘...this systematic review does not justify any change to clinical practice recommendations...’

Implications for research

The Royal College of Obstetricians and Gynaecologists has recommended [1] the use of either atosiban or nifedipine based on equivalent efficacy and superior safety compared with 3-agonists [2]. However:
- support for nifedipine largely comes from meta-analyses and systematic reviews of small, poorly conducted studies [3]
- there have been several recent reports of serious cardiovascular and pulmonary adverse events with nifedipine. [4-6]

The authors of this systematic review call for more research into the relative risks and benefits of atosiban vs nifedipine and placebo.

Nifedipine’s manufacturers actively discourage its use in preterm labour [7] and it is highly unlikely that such trials will be performed.

However, two recent studies have directly compared atosiban and nifedipine [8,9] and their findings are in agreement:
- atosiban and nifedipine have comparable efficacy
- atosiban is associated with significantly fewer adverse events and, in particular, cardiovascular adverse events.

Implications for practice

Although this review uses a sound search strategy and good-quality assessment of individual trials, the review covers a very small set of data which are pooled from, in some cases, very differently designed trials.

In particular, limitations of the two studies on which the key conclusions are based have a severe effect on the results. This, combined with low event rates, prevents any clear conclusion.

References


* Independent expert opinion.

Douglas Bedborough, Milton Keynes, Oxford, UK

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An expert’s view – ‘...the [placebo-controlled] trials were not similar enough in their clinical characteristics to be combined in a meta-analysis...’

‘...[the findings] do not justify any change to clinical practice recommendations...’

** APM Japan (branch office)
Interrogating the key findings
Efficacy versus placebo
These results are based on a single study that arguably should not have been included:
- sub-therapeutic doses of atosiban (TRACTOCILE) were given to women
- primary objective of the study was to evaluate the effect of atosiban on preterm uterine activity – ‘efficacy conclusions are invalid’.

Infant outcomes versus placebo
Most of the outcomes conclusions are based on a single study with severe limitations:
- widely acknowledged imbalance in treatment groups, with more women at very low gestational ages and in more advanced preterm labour receiving atosiban without the need for an alternative tocolytic, which evaluates both efficacy and tolerability of the study medication.

- despite this, most mortality parameters assessed were comparable with placebo.
- the increase in infant mortality only differed significantly from placebo when data up to 12 months of age were included.
- infant outcomes conclusions are invalid based on the available trial data; no atosiban trial has been designed to assess infant outcome.

Outcomes versus β-agonists
The only study that significantly favours β-agonists (birth weight < 1500 g) is not derived from the complete data set available:
- available data from two key trials are excluded.
- most endpoints favoured atosiban, including fetal, neonatal and perinatal death and maternal adverse drug reactions.

Atosiban (TRACTOCILE) has comparable efficacy to β-agonists at 48 hours, superior efficacy at 7 days and is associated with significantly fewer maternal adverse events

Critique of the main conclusions
Efficacy
- ‘atroiban was shown to have similar tocolytic efficacy to ... placebo.’
- efficacy data are taken from a single trial in which sub-therapeutic doses of atosiban (300 µg/min for 2 hours with no bolus) were used.
- data from the larger placebo-controlled trial were excluded from the efficacy analysis.
- birth within 48 hours is a less clinically relevant endpoint than non-delivery within 48 hours without the need for an alternative tocolytic, which evaluates both efficacy and tolerability of the study medication.

Infant outcomes
- ‘atroiban was associated with more infant deaths...’
- these data are from a single trial in which more women at extremely early gestational ages and more advanced labour (le women at higher risk) received atosiban (P = 0.008).
- at the time of the trial, the investigators stated that this imbalance may have accounted for the increased rate of fetal-infant deaths.
- subsequent trials have not demonstrated an increase in infant deaths.

Infant deaths were associated with extreme prematurity, not study medication.

The efficacy and safety of atosiban have been demonstrated in 742 women in randomised clinical trials and in a confirmed European clinical practice study in more than 800 women.*

An expert's view... ‘...this systematic review does not justify any change to clinical practice recommendations...’*

Implications for research
The Royal College of Obstetricians and Gynaecologists has recommended use of either atosiban or nifedipine based on equivalent efficacy and superior safety compared with β-agonists.** However:
- support for nifedipine largely comes from meta-analyses and systematic reviews of small, poorly conducted studies.
- there have been several recent reports of serious cardiovascular and pulmonary adverse events with nifedipine.

The authors of this systematic review call for more research into the relative risks and benefits of atosiban vs nifedipine and placebo.

Nifedipine’s manufacturers actively discourage its use in preterm labour* and it is highly unlikely that such trials will be performed.

However, two recent studies have directly compared atosiban and nifedipine and* their findings are in agreement:
- atosiban and nifedipine have comparable efficacy.
- atosiban is associated with significantly fewer adverse events and, in particular, cardiovascular adverse events.

Implications for practice
Although this review uses a search word strategy and good-quality assessment of individual trials, the review covers a very small set of data which are pooled from, in some cases, very differently designed trials.

In particular, limitations of the two studies on which the key conclusions are based had a severe effect on the results. This, combined with low event rates, prevents any clear conclusion.

References
Compared with placebo, more women receiving atosiban remain undelivered after 48 hours without the need for alternative tocolysis.1

The largest randomised controlled trials performed to date have demonstrated comparable trials, weights with β-agonists and have confirmed in a European clinical practice study in more than 7000 patients.2

Efficacy

- Atosiban (TRACTOCILE) has comparable efficacy to β-agonists at 48 hours, superior efficacy at 7 days and is associated with significantly fewer maternal adverse events.

Infant outcomes

- Atosiban was associated with more infant deaths...

- these data are from a single trial in which more women at extremely early gestational ages and more advanced labour (ie women at higher risk) received atosiban (P = 0.008 overall).

- at the time of the trial, the investigators stated that this imbalance may have accounted for the increased rate of fetal-infant deaths.

- subsequent trials have not demonstrated an increase in infant deaths.

Proposition of women remaining undelivered without the need for an alternative tocolytic at 48 h2

Infant deaths were associated with extreme prematurity, not study medication.3

The efficacy and safety of atosiban have been demonstrated in 742 women in randomised clinical trials and confirmed in a European clinical practice study in more than 800 women.4

An expert’s view: ‘...the findings do not justify any change to clinical practice recommendations...’

Implications for practice

Although this review uses a search work strategy and good quality assessment of individual trials, the review covers a very small set of data which are pooled from, in some cases, very differently designed trials. In particular, limitations of the two studies on which the key conclusions are based have a severe effect on the results. This, combined with low event rates, prevents any clear conclusion.

References


2. Independent expert opinions. Douglas Badenoch, Mimescience, Oxford, UK
