An evidence based approach for preterm labour management with a specific oxytocin antagonist

Tocolytics

- General considerations
- Beta-agonists
- Evidence pertaining to atosiban
- Concerns re nifedipine
- How has atosiban changed management
- Cost considerations
- Papatsonis systematic review

Aims of Tocolysis

- Appropriate use of time gained
  - Transfer to a tertiary care centre
Aims of Tocolysis

- Appropriate use of time gained
  - Transfer to a tertiary care centre
  - Administration of steroids
    - Pulmonary maturation
    - Reduction of RDS, IVH and NEC

Place of Delivery

<table>
<thead>
<tr>
<th></th>
<th>Neonatal Transfer</th>
<th>In-utero Transfer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>70% (166)</td>
<td>83% (212)</td>
</tr>
<tr>
<td>IVH</td>
<td>45% (119)</td>
<td>30% (207)</td>
</tr>
</tbody>
</table>


Benefits of Steroid Prophylaxis

- Steroids reduce perinatal morbidity & mortality

[Cochrane meta-analysis of 15 trials]
The great leap of faith

- Steroids reduce perinatal morbidity & mortality
- In utero transfer reduces perinatal morbidity & mortality

Tocolytic Myths

- Despite their use, the incidence of PTB has not changed for 20-30 years

- Steroids reduce perinatal morbidity & mortality
- In utero transfer reduces perinatal morbidity & mortality
- Delay in delivery must reduce perinatal morbidity & mortality

- BUT tocolytics have not been shown to be assoc with a reduction in perinatal mortality & morbidity
**Tocolytic Myths**

- Despite their use, the incidence of PTB has not changed for 20-30 years
- Effective for 48 hours only

**Unchanged rate of PTB**

- More babies at limits of viability

**Tocolytic Myths**

- Despite their use, the incidence of PTB has not changed for 20-30 years
- Effective for 48 hours only
- Do not reduce the incidence of perinatal mortality or morbidity

**Unchanged rate of PTB**

- More babies at limits of viability
- More elective PTB
Unchanged rate of PTB

- More babies at limits of viability
- More elective PTB
- Term birth should not be used as an outcome parameter

Each Day of Delay in Delivery Increases the Survival Rate by 3%

48 hour effectiveness

- Kierse meta-analysis

Completed gestation (weeks) [Finnstrom 1997]
48 hour effectiveness

- Kierse meta-analysis
- 48 hour measure common to included studies

48 hour effectiveness

- Kierse meta-analysis
- 48 hour measure common to included studies
- Many tocolytics effective for much longer than 48 hours

Reduction in Perinatal Mortality and Morbidity

- No tocolytic study ever powered to demonstrate a reduction in perinatal mortality/morbidity

Reduction in Perinatal Mortality and Morbidity

- No tocolytic study ever powered to demonstrate a reduction in perinatal mortality/morbidity
- Canadian Preterm Labour Investigators Group (600)
- Atosiban World Wide Comparative Study (800)
Reduction in Perinatal Mortality and Morbidity

- No tocolytic study ever powered to demonstrate a reduction in perinatal mortality/morbidity
- Canadian Preterm Labour Investigators Group (600)
- Atosiban World Wide Comparative Study (800)
- \text{LACK OF PROOF OF EFFECT DOES NOT MEAN PROOF OF LACK OF EFFECT}

Choice of Tocolytics

\textbf{Licensed Preparations}
- Beta-agonists (Ritodrine, Terbutaline, Salbutamol, Fenoterol)
- Anti-oxytocics (Atosiban)

\textbf{Unlicensed Preparations}
- NO donors (GTN)
- PG-synthetase inhibitors (Indomethacin, Sulindac, COX-2)
- \textit{Magnesium sulphate}
- Ca channel blockers (Nifedipine, Nicardipine)

Choice of Tocolytics

\textit{Specifically developed to be uterospecific/SPTL}
- Anti-oxytocics (Atosiban)
- Few side effects

\textit{Not specifically developed}
- NO donors/NSAIDs/MagSulph/CCB/Beta-agonists
- Not uterospecific
- Multi-organ side effects

Beta -agonists
Pathophysiology of Pulmonary Oedema with the Use of Beta-agonists

Incidence: 0.3% to 9% of women receiving beta-agonists

Factors Associated with Pulmonary Oedema
- Maternal
- Fetal
- Tocolytics
- Fetomaterna infection

A review article

Factors Associated with Pulmonary Oedema (2)

- Tocolytic
  - Positive fluid balance
    - Drug induced fluid retention
    - Iatrogenic fluid overload
  - Cardiovascular effects
  - Metabolic effects
  - Concomitant use of glucocorticoids

Monitoring Beta-agonist Therapy

- Maternal pulse and BP every 15 minutes
- Blood sugar every 4 hours
- Strict record of fluid balance (input/output)
- Daily Us and Es
- Auscultation of lung fields every 4 hours

RCOG Guidelines
The worries concerning side effects of tocolytics has resulted in limitations in their use.

Historical limitations in the use of tocolytics
- Not < 24 weeks gestation
- Not > 34 weeks gestation

- Not > 48 hours duration
**Historical limitations in the use of tocolytics**

- Not < 24 weeks gestation
- Not > 34 weeks gestation
- Not > 48 hours duration
- Not for prophylaxis
- Not for maintenance
- Not until certain of diagnosis

**Prolongation of gestation – Bishop score**

<table>
<thead>
<tr>
<th>Prolongation of Gestation (days)</th>
<th>&lt; 2</th>
<th>2–6</th>
<th>7–13</th>
<th>14–20</th>
<th>21–27</th>
<th>28–55</th>
<th>&gt; 55</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Bishop Score</td>
<td>8.0</td>
<td>5.9</td>
<td>5.3</td>
<td>5.5</td>
<td>4.5</td>
<td>3.6</td>
<td>3.5</td>
</tr>
</tbody>
</table>
How would that change if we had a tocolytic which was safe to use for mother & fetus?

Anti-oxytocic tocolytics

Molecular Mechanism of Muscle Contraction

Tractocile®: Oxytocin Receptor Antagonism in the Uterus
Worldwide comparative trials of atosiban in the treatment of preterm labour

Ronald Lamont MD FRCOG
Consultant/Reader, Northwick Park & St Marks Hospitals, and Imperial College School of Medicine, London UK

Summary

- Largest clinical trial of tocolytic therapy
- Strict inclusion/exclusion criteria
- Atosiban at least as effective as beta-agonists
- Similar safety profile for neonates
- Significantly safer for women, particularly cardiovascular side effects

Multinational centres

- Canada: 6
- France: 31
- UK: 12
- Denmark: 2
- Sweden: 7
- Czech Republic: 6
- Israel: 7
- Australia: 6

Compared with 3 beta-agonists

- Ritodrine: Canada and Israel (15)
- Terbutaline: UK, Sweden, Denmark, Czech Republic (27)
- Salbutamol: France and Australia (37)

Same protocol/individual study reports/pooled data
Patient population

742 women recruited to study
- atosiban, n = 363
- beta-agonists, n = 379

Methodology

- Contractions & Cx length & Dilation
- Washout for other tocolytics
- Stratified randomisation around 28w
- Alternative tocolytic therapy
- Retreatment

Worldwide comparative Study

Efficacy and Tolerability

(No additional tocolytics/undelivered after 7 days)
Efficacy

Clinical safety – maternal I

Clinical safety – maternal II

Clinical safety – maternal III
Concerns re nifedipine

- No PCTs
- No FU studies
- Evidence from meta-analysis
  - unblinded
  - no ITT analysis
  - lack sufficient power
  - late gestations
  - no account of randomisation
  - used as second line treatment

Concerns re nifedipine Contd

- Difficult to confirm or refute hypotension or PO in normotensive patients since sample size of published data too small
- Same applies to sole or combined use
- Different preparations not usually stipulated

Life after Beta-agonists

Background

RCOG: tocolytic drugs for women in preterm labour
Clin Guidelines No 1 (B) 2002
Atosiban v Nifedipine
### Quality of Nifedipine Studies

- Dose and preparation unclear
  - Sublingual/oral/chewing
  - Tablets/capsules
  - Slow release/long acting
- Often combination/2nd line therapy
  - Potentiates adverse events

### Nifedipine Studies-the evidence

2 Meta-analyses:
- Tsatsiris et al, Obstet Gynecol 2001; 97: 840

2 Systematic Reviews
- King et al, Cochrane Database Syst Rev 2003; CD002255

### Concerns re quality of Nifedipine Studies

- Meta-analyses retrospective analysis of pooled data
- Only as good as quality of studies included
- Suitable for large number of good quality contradictory studies, eg PPROM
- Not suitable for small number of poor quality studies

### Birth <7 days

<table>
<thead>
<tr>
<th>Study</th>
<th>Weight</th>
<th>RR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koks 1998</td>
<td>16.4</td>
<td>1.14</td>
<td>(0.7, 1.8)</td>
</tr>
<tr>
<td>Larmon 1999</td>
<td>6.3</td>
<td>0.38</td>
<td>(0.1, 1.8)</td>
</tr>
<tr>
<td>Papatsonis 1997</td>
<td>60.2</td>
<td>0.66</td>
<td>(0.5, 0.9)</td>
</tr>
<tr>
<td>Weerakul 2002</td>
<td>17.1</td>
<td>0.91</td>
<td>(0.5, 1.7)</td>
</tr>
<tr>
<td>Total</td>
<td>100.0</td>
<td>0.76</td>
<td>(0.6, 0.97)</td>
</tr>
</tbody>
</table>

- Favours nifedipine: 1.0
- Favours any other tocolytic

King et al, Cochrane, 2003
Letter to Bayer Pharmaceuticals re nifedipine

- Licenced for use in pregnancy?
- Indicated for use in SPTL?
- Published data to support use in SPTL?
- Safety worries?
- Response to RCOG draft guidelines?
- Responsibility for adverse effects?

Reply from Bayer Pharmaceuticals

- Does nifedipine have a licence for use in pregnancy?
  - No!
- Does nifedipine have a licence for use in SPTL?
  - No!
- What is the evidence to support the use of nifedipine in SPTL?
  - Small, poor quality, investigator led studies!
Reply from Bayer Pharmaceuticals

- Does nifedipine have a licence for use in pregnancy?  
  - No!
- Does nifedipine have a licence for use in SPTL?  
  - No!
- What is the evidence to support the use of nifedipine in SPTL?  
  - Small, poor quality, investigator led studies!
- What are the worries about safety?  
  - List of case reports etc held on file @ Bayer

Why not do a systematic review of quality?

- Not to recommend nifedipine! Any queries to RCOG!
The quality of nifedipine studies used to assess tocolytic efficacy: A systematic review


Acknowledgements
Goodwin TM (USA) Tsatsiris V (Fra) McNamara H (Can)

The International Preterm Labour Council

Methods

- Forty-five studies were identified
  - five conference abstracts were unavailable
  - three conference abstracts were superseded by full articles
  - six trials were excluded on grounds of irrelevance
  - one article was excluded because it did not compare a calcium channel blocker

- Thirty-one studies were analysed
- Items of quality assessed
  - method-specific (generic)
  - topic-specific
  - 40 quality items assessed

Study Design

- Selection bias
  - Randomisation
  - Concealment
- Performance bias
  - Standardisation of care protocol
  - Blinding of care providers and patients
- Measurement bias
  - Blinding of outcome assessors and patients
  - Intention to treat analysis

Generic Quality Items

- Intention to treat analysis
- Randomisation
- Concealment
- Standardisation of care protocol
- Blinding of care providers and patients
- Blinding of outcome assessors and patients

Population

- Study sample
- Allocation of subjects
- Control
  - Intervention
- Experimental
  - Intervention
- Follow up
- Outcome Present/Absent
- Outcome Present/Absent
- Effect size

Interventions

- Study Design
  - Selection bias
    - Randomisation
    - Concealment
  - Performance bias
    - Standardisation of care protocol
    - Blinding of care providers and patients
  - Measurement bias
    - Blinding of outcome assessors and patients
    - Intention to treat analysis

Outcomes
Study sample

Control

Intervention

Experimental Intervention

Allocation of subjects

Randomisation

Concealment

• Standardisation of care protocol
  • Blinding of care (providers and patients)

• Drug route, dose, type and preparation of first choice agent
  • Use of second-line agent or combined use
  • Maintenance or retreatments
  • Administration of complete course steroids
  • In utero transfer

Experimental intervention

Follow up

Follow up

Outcome Present/Absent

Blinding of outcome (assessors and patients)

• Adequate ascertainment of gestational age
  • Complete follow up

Effect size

• Cervical effacement, dilatation, uterine contractions
  • Intact membranes, multiples
  • Parity, age, race, socioeconomic, gestational age at study entry
  • History of late miscarriage, preterm birth, substance abuse, smoking

Follow up

Outcome Present/Absent

Effect size

Distribution on a scale from 0 to 100%

Selection bias

Performance bias

Measurement bias

Overall

Compliance with method- and topic-specific items

Method-specific

Selection bias

Performance bias

Measurement bias

Overall

0 20 40 60 80 100

<table>
<thead>
<tr>
<th>Adequate</th>
<th>Unclearly reported</th>
<th>Inadequate</th>
</tr>
</thead>
</table>

Effect size

Quality of nifedipine studies

Selection bias

Inadequate concealment of allocation (77%)

No stratified randomisation (97%)

Performance bias; blinding to treatment (94%)

Measurement bias; blinding to outcome (100%)

Attrition bias; intention-to-treat analysis (71%)

( ) : refers to inadequate or not stated

From: Lamont et al. The quality of…nifedipine trials;

Conclusions

• Compliance with individual measures of quality was poor

• Overall compliance was poorer with method-specific items compared with topic-specific items
  – 11.5% versus 27.5%; P < 0.0001

• When compared directly, compliance was poorer with method-specific items compared with topic-specific items
  – selection bias (10.8% versus 27.8%; P < 0.0001)
  – performance bias (3.2% versus 29.5%; P < 0.0001)

• There was no improvement in quality over time

• Guidelines may be unduly influenced by such studies
  – recommendations should be moderated in light of methodological deficiencies
Concerns re Safety of Nifedipine

- Benefits of oral admin compromised by duration of onset
- Rapid onset associated with severity of side effects
- Slow release – fewer side effects but delayed action, temptation to use additional tocolytics
- Problems mainly with rapid release
  Sublingual/chewing capsules/“prick ‘n’ spray”

Recent Concerns on Safety of Nifedipine

**Pulmonary Edema**

**Myocardial Infarction**
- Verhaert et al, Acta Cardiol 2004; 59: 331-339 (Belgium)

**Hypotension and Fetal Death**
- van Veen, BJOG; 2005; 112: 509-10 (Holland)

**Maternal Hypoxia**
- Hodges et al BJOG, 2004; 111: 380-1 (Australia)

### Reported adverse cardiovascular effects in association with nifedipine or other CCB's

<table>
<thead>
<tr>
<th>Author</th>
<th>Complication</th>
<th>Tocolytic</th>
<th>Other medication</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oei 1999</td>
<td>myocardial infarction (1)</td>
<td>nifedipine 3 times 40 mg</td>
<td>ritodrine</td>
<td>healthy, normal ECG</td>
</tr>
<tr>
<td>Hodges 2004</td>
<td>maternal hypoxia, ventilation (1)</td>
<td>nifedipine twice 20 mg</td>
<td>cortico's</td>
<td>asymptom. VSD, normal ECG</td>
</tr>
<tr>
<td>Verhaert 2004</td>
<td>myocardial infarction (1)</td>
<td>nifedipine 3 times 20 mg</td>
<td>ritodrine cortico's</td>
<td>healthy, normal ECG</td>
</tr>
<tr>
<td>Vaast 2004</td>
<td>acute pulmonary oedema (5)</td>
<td>nicardipine 60–140 mg i.v.</td>
<td>cortico's</td>
<td>twin (2), triplet, mitral valve, diabetes</td>
</tr>
</tbody>
</table>
Cardiovascular actions of nifedipine

**Vessels (10):**
- vaso-dilation

**Heart (1):**
- negative inotrope
- negative chronotrope

*Vascular/cardiac ratio

Scholz H. Cardiovasc Drugs Ther 1997; 10: 869–72

“Healthy” individual

1. vaso-dilation by nifedipine
2. baroreceptor stimulation
3. increase in sympathetic tone
4. compensates for cardio-depression

Twins, infection

maximum vaso-dilation plus nifedipine

baroreceptor stimulation
increase in sympathetic tone
carotid sinus
aortic arch

cardio-depression
Twins, infection
maximum vaso-dilation plus nifedipine

baroreceptor stimulation

increase in sympathetic tone

Cardiac disease (pulmonary hypertension, cardiomyopathy)
diminished cardiac output plus nifedipine

hypotensive negative inotrope negative chronotrope

Nifedipine for tocolysis

• Seemingly attractive
  – Oral, cheap, few side effects

• Not registered for use in pregnancy
  – Especially not tocolysis
    • Therefore side effects may be under reported
  – Licensed alternatives available

• Studies are small and suffer from a number of biases
  – Selection, allocation, performance, measurement, attrition bias

Nifedipine for tocolysis

• Potential negative effects on cardiovascular functioning
  – Hypotension, oedema formation, cardio-depression
  – Tocolytic available with placebo-level cardiovascular risk

• Caution advised for use of nifedipine in pregnancy, particularly if confronted with a "non-normal" course
  – Avoid immediate release preparations and high dosages

How has Tractocile changed management?

• Change in risk-benefit analysis
  – Primum non nocere/therapeutic nihilism

• Debate on:
  – Cost vs safety
  – License vs non-license preparation

• Raised issues of:
  – Clinical governance
  – Risk management/medical legal implications

• Implications on future management of preterm labour
The worries concerning side effects of tocolytics has resulted in limitations in their use. How would that change if we had a tocolytic which was safe to use for mother & fetus?

New opportunities for the use of tocolytics:
- < 24 weeks gestation
- > 34 weeks gestation
- > 48 hours duration
- Use for prophylaxis
- Use for maintenance
- Use early in threatened SPTL
- Might improve efficacy

Cost considerations in relation to:
- Total cost of PTB
Cost of Preterm Birth

- Cost of neonatal intensive care (USA)
  - Weekly: $10,000 per baby
  - Graduation from NICU: $20-100,000 per infant
  - Annual: >$5 billion

- Long-term costs (USA)
  - Severe handicap: >$100,000
  - Lifelong residential care: $450,000

[Keirse, 1995]

Mean hospital costs during first 10 years of life (£ UK 1998 prices)*

<table>
<thead>
<tr>
<th>Years 1-5</th>
<th>&lt; 28 w</th>
<th>28-31 w</th>
<th>32-36 w</th>
<th>≥ 37 w</th>
<th>P value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>6th year</td>
<td>192.6</td>
<td>80.0</td>
<td>79.2</td>
<td>53.3</td>
<td>0.0178</td>
</tr>
<tr>
<td>7th year</td>
<td>155.6</td>
<td>95.1</td>
<td>62.0</td>
<td>48.3</td>
<td>0.1257</td>
</tr>
<tr>
<td>8th year</td>
<td>73.6</td>
<td>131.1</td>
<td>57.6</td>
<td>35.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>9th year</td>
<td>155.1</td>
<td>72.1</td>
<td>37.2</td>
<td>31.4</td>
<td>0.0256</td>
</tr>
<tr>
<td>10th year</td>
<td>57.2</td>
<td>53.7</td>
<td>33.5</td>
<td>27.1</td>
<td>0.1656</td>
</tr>
</tbody>
</table>

| Years 1-10 | 13184.3 | 10250.1 | 3012.7 | 759.4 | <0.0001 |

** ANOVA

Cost considerations in relation to:

- Total cost of PTB
- Other budgets-onco/psyche/fertil/cardiol
- Other tocolytics-20 x peanuts=peanuts
Cost considerations in relation to:

- Total cost of PTB
- Other budgets-onco/psyche/fertil/cardiol
- Other tocolytics-20 x peanuts=peanuts
- Midwifery time
- Medicolegal liability(evidence/licence/Borman)
- Safety
“similar efficacy to placebo”

- Single trial
- Threatened PTL
- Sub therapeutic doses
- Romero study not included

**Tractocile®: Phase II Studies**

- **Goodwin et al (1994)**
  - **Design**
    - Randomised, placebo-controlled study
    - 120 women, 20-36 weeks, threatened preterm labour
    - 300μg/min atosiban for 2 hours
  - **Results**
    - % decrease in uterine contractions: 55.3% atosiban vs 26.7% placebo, p=0.001
    - Complete cessation of contractions: 25% atosiban vs 5% placebo, p=0.007
    - AEs with atosiban: nausea and vomiting
  - **Conclusion**
    - Atosiban reduces uterine contraction rate in women in preterm labour and atosiban is well tolerated

**US Phase III Studies: PTL-096**

<table>
<thead>
<tr>
<th>% Women undelivered and no alternative tocolytic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atosiban (n =246)</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>24 hrs.</td>
</tr>
<tr>
<td>48 hrs.</td>
</tr>
<tr>
<td>7 days</td>
</tr>
</tbody>
</table>

- Atosiban vs Placebo:
  - p < 0.001*
  - p=0.008*
  - p=0.003*

*Cochran-Mantel-Haenszel test, stratified by centre

**Similar tocolytic efficacy to beta-agonists**

- Omitted pooled data
- Selected 48h not 72h (Moutquin)
- Included dose ranging study
Tractocile®: Phase II Studies

- Goodwin et al (1996b)
  - Design
    - Randomised, comparative study
    - 302 women, 20-35 weeks, preterm labour
    - 4 dosage regimens of atosiban for up to 12 hours, ritodrine given according to product labelling
  - Results
    - 3 of 4 doses of atosiban comparable to ritodrine
    - 6.5mg bolus + 300μg/min most effective (p<0.02)
    - More women discontinued with ritodrine (p<0.001)
  - Conclusion
    - Atosiban was comparable to ritodrine in treating preterm labour but with significantly fewer side effects

"Increased infant mortality"

- One trial only included
- Perinatal neonatal fetal not affected
- Two deaths counted twice
- Higher proportion before 26 weeks
- Atosiban 24/246 (10%)
- Placebo 13/255 (5%)
- Not confirmed in other studies
- Not confirmed in 70,000 treatments

Partially & bias

- Authors self appointed
- Advocates of nifedipine
- No experience of atosiban
- Reflects their clinical preference
- Methodological concerns

Overall methodological concerns

- Selective inclusion/exclusion of trials
- Abstract poor reflection of main text
- Extension beyond review objectives