Review of efficacy & safety of nifedipine as tocolytic in late pregnancy.

Definition
Preterm birth is the birth occurring between 20 and 36 weeks of gestation. It is a major contributor to perinatal mortality and morbidity, and affects 6-7% of births in developed countries1.

Currently there is 1 item for tocolysis on the WHO EML, Section 22. Oxytocics and antioxytocics:

22.2 Antioxytocics
   • salbutamol, tablet, 4 mg (as sulfate) and injection, 50 µg (as sulfate) in 5-ml ampoule
with the footnote stating: "The public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion in the Model List will be reviewed at the next meeting of the Expert Committee."

Nifedipine is listed on the WHO EML, Section 12. Cardiovascular medicines:
   12.3 Antihypertensive medicines
   • nifedipine, sustained-release formulations tablet 10 mg

Nifedipine is listed on the Anatomical Therapeutic Chemical (ATC) classification index with Defined Daily Doses (DDDs) (WHO Collaborating Centre for Drug Statistics Methodology), Oslo, Norway, 2004 under section C08 Calcium channel blockers – C08C A05 Nifedipine.

The application for listing of Nifedipine, regular tablets or capsules 10mg and 20 mg, as tocolytic is supported by strong clinical evidence of its superiority to betamimetics and magnesium sulfate in acute tocolysis – inhibiting preterm labour. The effects of nifedipine in suppression of preterm labour were critically assessed and summarised in a meta-analysis2 and a Cochrane Systematic Review3.

Meta-analysis of nifedipine versus ritodrine for suppression of preterm labour concluded that nifedipine should be the drug of choice for the suppression of pre-term labour (positive commentary of the NHS Centre for Reviews and Dissemination (CRD) of the Cochrane collaboration for the published pooled analysis)4.

Nifedipine was studied in ten out of twelve randomised controlled trials included in the Cochrane Review involving totally 1029 women. Nifedipine was compared with betamimetics (ritodrine and terbutaline (1 trial)) and magnesium sulfate (1 trial). Nicardipine was another calcium channel blocker assessed in this review.

Efficacy of tocolysis.
The advantage in efficacy of nifedipine (calcium channel blockers) vs betamimetics or magnesium sulfate was characterised by:
   • reduction of the number of women giving birth within seven days of receiving treatment (relative risk (RR) 0.76 with 95% Confidence interval (CI) 0.60 to 0.97);
   • reduction of the number of women giving birth prior to 34 weeks of gestation (RR 0.83; 95% CI 0.69 to 0.99).
Efficacy in terms of neonatal outcomes.
Nifedipine (calcium channel blockers) demonstrated the major advantage over traditionally used tocolytics (betamimetics and magnesium sulfate) in its favourable effects on neonatal outcomes characterised by reduction of the frequency of:

- neonatal respiratory distress syndrome (RR 0.63; 95% CI 0.46 to 0.88),
- necrotising enterocolitis (RR 0.21; 95% CI 0.05 to 0.96),
- intraventricular haemorrhage (RR 0.59 95% CI 0.36 to 0.98)
- and neonatal jaundice (RR 0.73; 95% CI 0.57 to 0.93).

Maternal side effects.
Nifedipine (calcium channel blockers) proved much better overall safety profile compared with betamimetics and magnesium sulfate, documented by reduction in the requirement for women to have treatment ceased due to adverse drug reaction (RR 0.14; 95% CI 0.05 to 0.36),

Later clinical trial confirmed the conclusion about superiority of nifedipine in efficacy and safety in inhibiting preterm labour5,6.

Maintenance therapy in tocolysis.
Benefits and harms of maintenance therapy for preventing preterm birth after threatened preterm labour with calcium channel blockers as well as with other tocolytics remain unclear7,8,9,10,11 and further research is warranted (Cochrane Systematic Review12 based on the results of 1 trial13).

Conclusion
High quality clinical evidence has accumulated to form a convincing argument to list nifedipine as an antioxytocic (tocolytic) for inhibiting preterm labour, tablets, capsules, 10 milligrams; 20 milligrams on the WHO Model List of Essential Medicines.

The following additions are suggested to the text for the WHO Model Formulary:

Tablets, nifedipine 10 mg, 20 mg (for acute tocolysis)
Capsules, nifedipine 10 mg, 20 mg (for acute tocolysis)

In Uses: uncomplicated premature labour between 20-33 weeks of gestation as acute tocolysis.
In Dose (based on the largest trial with the most favourable outcomes)14: Premature labour for acute tocolysis, ADULT initially sublingually, 10 milligrams, repeated every 20 minutes to maximum dose of 40mg in the first hour. Once contractions ceased 20 milligrams every 4 hours for 48 hours, then maintenance (orally) 10 milligrams every 8 hours until 34 weeks of gestation.

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