Frequently asked questions on tocolytics

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The majority of drugs that are used today for tocolysis have been developed for clinical conditions other than preterm labour. Obstetricians started to use these drugs as tocolytics because of their additional influence on uterine smooth muscle relaxation, accepting their cardiovascular (side) effects. Because the majority of these drugs are used off label, today’s strict criteria to evaluate drugs for their predominant use in pregnancy have not been applied; therefore, we also lack sufficient peri- and neonatal follow up data for these drugs. This problem is compounded as our understanding of the regulation of myometrial smooth muscle contraction and relaxation is still incomplete.

INTRODUCTION

The Clinical Green-Top Guidelines of the Royal College of Obstetricians and Gynaecologists1 state that there is no clear evidence that the use of tocolytic drugs improves neonatal outcomes. There are several possible explanations for this. Firstly, the meta-analysis by Gyetvai et al.2—the most frequently cited systematic review concerning tocolytic effectiveness and safety to date—included 1434 patients spread over 18 trials, with an average of only 80 patients per trial. Studies of this size do not have the statistical power to detect significant differences in important neonatal outcomes. Secondly, in many studies the proportion of patients receiving antenatal corticosteroids is small or unspecified. Thirdly, the majority of studies include women presenting at up to 34–35 weeks of gestation, which decreases the power to detect significant differences in neonatal outcomes. However, as the Royal College concludes, tocolysis should be considered if the few days gained would be put to good use, such as completing a course of corticosteroids, or in utero transfer.

FIRST-LINE TOCOLYTIC DRUG

The American College of Obstetricians and Gynecology (ACOG) gives this general recommendation for the use of tocolytic medication in the clinical management of preterm labour: “If tocolytic drugs are used, the choice of drug should be individualised and based on maternal condition, potential drug side effects, and gestational age”. The ACOG also comments on the combined use of tocolytic drugs: “Combining tocolytic drugs potentially increases maternal morbidity and should be used with caution”.

The Agency for Healthcare Research and Quality, representing the health services research arm of the U.S. Department of Health and Human Services, states in its Evidence Report/Technology Assessment: Number 18: Management of Preterm Labor: “Beta-mimetics, calcium channel blockers, magnesium sulphate, or non-specific non-steroidal anti-inflammatory drugs (NSAIDs) offer small improvements in prolonging pregnancy”. (The oxytocin antagonist, atosiban, is not licensed in the United States.) With regards to the adverse effects of tocolytics, the report states: “We graded beta-mimetics as ‘high’ in probability of maternal risk, including serious cardiovascular harms, metabolic harms, and psychological harms”. The guidelines of the local gynaecological organisations of some European Union countries recommend the use of atosiban in patients with diabetic conditions or heart problems because of the cardiovascular side effects of β-agonist drugs. However, in general, there are no recommendations about which tocolytic is appropriate to use for a particular subgroup of pregnant women suffering from preterm labour. Following the medical principle primum non nocere (‘first, do no harm’), the drug with the least side effects should be used. In Europe, this condition is best accomplished by atosiban.

MAINTENANCE THERAPY

Magnesium maintenance therapy is one of the types of tocolytic therapy used after an episode of threatened preterm labour in an attempt to prevent the onset of further preterm contractions. According to a Cochrane review,3 there is not enough evidence to show any difference between magnesium maintenance therapy and either placebo or no treatment, or alternative therapies (ritodrine or terbutaline) in preventing preterm birth after an episode of threatened preterm labour. Moreover, magnesium sulphate is ineffective at delaying birth or preventing preterm birth, and its
use is associated with an increased mortality rate for the infant. Terbutaline pump maintenance therapy has also failed to decrease the risk of preterm birth by prolonging pregnancy.

Although there seems to be a trend that uterine quiescence could be prolonged by subcutaneous atosiban application compared with placebo, at present we cannot recommend its clinical use in maintenance therapy.

MULTIPLE PREGNANCY

It is difficult to find clinical evidence for tocolytic treatment in multiple pregnancies. In general, the obstetrician has to be aware that this is a very different situation from that of the singleton with intact membranes. The use of corticosteroids to induce lung maturation in twins or multiple pregnancies induces uterine contractions, often treated by tocolysis. Conversely, it has not been demonstrated that lung maturation significantly reduces the rate of respiratory distress syndrome in multiple pregnancies. The decision to administer antepartum corticosteroids to induce fetal lung maturation has to be taken carefully. Apart from the sonographic evaluation of the cervical length, determination of an elevated cervicovaginal fetal fibronectin level is also recommended in multiple pregnancies with intact membranes. In a study by Wennerholm et al., all positive fetal fibronectin samples obtained from screening between 24 and 34 weeks predicted birth <35 weeks. In the same study, a positive fetal fibronectin sample at 28 weeks of gestation predicted neonatal morbidity (relative risk [RR] 5.1; 95% CI 2.4–11.0) and a longer period of care in the neonatal intensive care unit.

Women with multiple pregnancies are more likely to develop hypervolemic conditions. This increases their chance of suffering from pulmonary oedema, associated with the use of β-agonists as tocolytics. As a result, some national guidelines suggest atosiban as the first-line tocolytic of choice. Little data exist concerning the use of calcium channel blockers in multiple pregnancies, but recent publications report an increase in pulmonary oedema in instances where the calcium channel blocker nicardipine has been used.

PRETERM PREMATURE RUPTURE OF MEMBRANES

In the presence of preterm prelabour rupture of membranes (PPROM), no study to date has demonstrated that tocolytics improve or worsen neonatal outcome, but these have not evaluated tocolysis when corticosteroids and antibiotics are administered concurrently. Short term pregnancy prolongation with tocolysis could enhance the potential for corticosteroids and could allow more time for antibiotics to act against subclinical decidual infection.

INTRAUTERINE RESUSCITATION

In many European obstetric institutions intrauterine resuscitation is routinely performed by using β-agonist drugs to treat fetal distress during labour, usually caused by cord complications or abnormal contractions. A recent randomised controlled trial evaluated the use of atosiban in this situation. Women with a gestational age of more than 38 weeks presenting with a diagnosis of intrapartum fetal distress (severe fetal bradycardia) requiring intrauterine resuscitation were included. Thirteen women were randomised to receive atosiban and 13 women received hexoprenaline. The results of this pilot study found that the administration of an intravenous bolus of hexoprenaline or atosiban resulted in a rapid improvement of the fetal heart rate in nearly all the women. There were significantly fewer maternal side effects in the atosiban group. The authors of the study conclude that atosiban may be an attractive alternative for the treatment of intrauterine resuscitation.

UTERINE RELAXATION BY NITRIC OXIDE (NO)

Data from human and experimental animal research indicate that NO is involved in maintaining normal uterine tone during gestation. Therapeutic indications for NO range from facilitating external cephalic version, difficult vaginal or caesarean section delivery and manual exploration of the uterus, to its use as a tocolytic. Methods of NO administration include intravenous administration and sublingual spray. When used in low doses, NO may provide safe and effective short time uterine relaxation with no clinically apparent fetal or maternal adverse effects.

Its routine use as a tocolytic drug until now cannot be recommended because we lack studies with sufficient patient numbers and adequate long term infant follow up results.

FUTURE ASPECTS

Recent trends have favoured agents with lower maternal side effect profiles, including calcium channel blockers and the oxytocin receptor antagonist atosiban. Several inhibitors of cyclooxygenase-2 (COX-2), the enzyme required to produce the prostaglandins most likely involved in preterm labour, have been developed. These agents—so-called ‘coxibs’—may be more effective tocolytics or exhibit a better side effect profile than the NSAIDs currently used.

Future directions in tocolytic research include the possible use of multiple-agent therapies, along with the development of more selective treatments with low side effect profiles. Such agents with more favourable pharmacological properties include prostaglandin F2α receptor antagonists and oxytocin antagonists.
A newly developed oxytocin antagonist, FE 200 440, named barusiban, has a high affinity for the human cloned oxytocin receptor, approximately 300-fold that for the vasopressin V(1a) receptor. In contrast to atosiban, barusiban has practically no effect on vasopressin-induced contractions of isolated term pregnant human myometrium. Depending on its concentration, barusiban inhibits oxytocin-induced myometrial contractions of both preterm and term myometrium at least as potently as atosiban. It remains to be determined if the selectivity of barusiban for the oxytocin receptor confers an advantage over atosiban as a tocolytic in preterm labour.

Future research into tocolytic therapies must focus on evaluating the health outcomes of treatments rather than simply the ability to prolong pregnancy, and consequently the design of appropriate clinical studies needs careful consideration with respect to issues such as inclusion criteria, sample size and the selection of appropriate outcome measures.

References
