OBSTETRICS

Low-dose betamethasone-acetate for fetal lung maturation in preterm sheep

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BACKGROUND: Antenatal steroids are standard of care for women who are at risk of preterm delivery; however, antenatal steroid dosing and formulation have not been evaluated adequately. The standard clinical 2-dose treatment with betamethasone-acetate+betamethasone-phosphate is more effective than 2 doses of betamethasone-phosphate for the induction of lung maturation in preterm fetal sheep. We hypothesized that the slowly released betamethasone-acetate component induces similar lung maturation to betamethasone-phosphate+betamethasone-acetate with decreased dose and fetal exposure.

OBJECTIVE: The purpose of this study was to investigate pharmacokinetics and fetal lung maturation of antenatal betamethasone-acetate in preterm fetal sheep.

STUDY DESIGN: Groups of 10 singleton-pregnant ewes received 1 or 2 intramuscular doses 24 hours apart of 0.25 mg/kg/dose of betamethasone-phosphate+betamethasone-acetate (the standard of care dose) or 1 intramuscular dose of 0.5 mg/kg, 0.25 mg/kg, or 0.125 mg/kg of betamethasone-acetate. Fetuses were delivered 48 hours after the first injection at 122 days of gestation (80% of term) and ventilated for 30 minutes, with ventilator settings, compliance, vital signs, and blood gas measurements recorded every 10 minutes. After ventilation, we measured static lung pressure-volume curves and sampled the lungs for messenger RNA measurements. Other groups of pregnant ewes and fetuses were catheterized and treated with intramuscular injections of betamethasone-phosphate 0.125 mg/kg, betamethasone-acetate 0.125 mg/kg, or betamethasone-acetate 0.5 mg/kg. Maternal and fetal betamethasone concentrations in plasma were measured for 24 hours.

RESULTS: All betamethasone-treated groups had increased messenger RNA expression of surfactant proteins A, B, and C, ATP-binding cassette subfamily A member 3, and aquaporin-5 compared with control animals. Treatment with 1 dose of intramuscular betamethasone-acetate 0.125mg/kg improved dynamic and static lung compliance, gas exchange, and ventilation efficiency similarly to the standard treatment of 2 doses of 0.25 m/kg of betamethasone-acetate+betamethasone-phosphate. Betamethasone-acetate 0.125 mg/kg resulted in lower maternal and fetal peak plasma concentrations and decreased fetal exposure to betamethasone compared with betamethasone-phosphate 0.125 mg/kg.

CONCLUSION: A single dose of betamethasone-acetate results in similar fetal lung maturation as the 2-dose clinical formulation of betamethasone-phosphate+betamethasone-acetate with decreased fetal exposure to betamethasone. A lower dose of betamethasone-acetate may be an effective alternative to induce fetal lung maturation with less risk to the fetus.

Key words: antenatal corticosteroids, betamethasone, fetal lung maturation, prematurity

Antenatal corticosteroids (ANS) are a life-saving therapy for premature infants. Despite the well-documented effectiveness and widespread use, questions remain regarding formulation, dosing, route of administration, and repeated doses[1] because the ANS used for fetal lung maturation has not been evaluated rigorously.[2] In fact, multiple treatments are used around the world based on drug availability and historical use without experimental or clinical evaluation.[3] The most commonly recommended and tested regimens are intramuscular dexamethasone-phosphate 6 mg every 6 hours for 4 doses (total dose 24 mg) or the combination of betamethasone-acetate (Beta-Ac) and betamethasone-phosphate (Beta-P) 12 mg every 24 hours for 2 doses.[4-6] The maturational effects of ANS likely are determined by the length and amplitude of fetal exposure. Although several formulations are used interchangeably, the pharmacokinetics profiles of the formulations are different and may not all be equally effective.

The 2-dose regimen of Beta-Ac+Beta-P was used by Liggins and Howie[7] in their seminal trial and has been adopted as the standard therapy for most randomized controlled trials.[8] The Beta-P component is dephosphorylated rapidly to the active drug, which, in the sheep model, results in an early maternal peak concentration of approximately 130 ng/mL at <1 hour, with a half-life of 4 hours.[9,10] The microparticulate Beta-Ac component is slowly deacetylated, which results in a later peak and more prolonged half-life compared with the phosphate component. The clinical combination of the 2 drugs results in a complex pharmacokinetics with a half-life of 14 hours.[10] Drug levels in humans are limited to paired maternal and cord blood fetal samples that are collected from deliveries shortly after an ANS treatment. An estimate of the initial half-life in maternal plasma was 9 hours with peak maternal levels of betamethasone at 3−4 hours of approximately 60 ng/mL and fetal plasma beta levels of approximately 30% of maternal levels.[11] In contrast, in preterm sheep a single Beta-Ac dose of 0.25 mg/kg promotes

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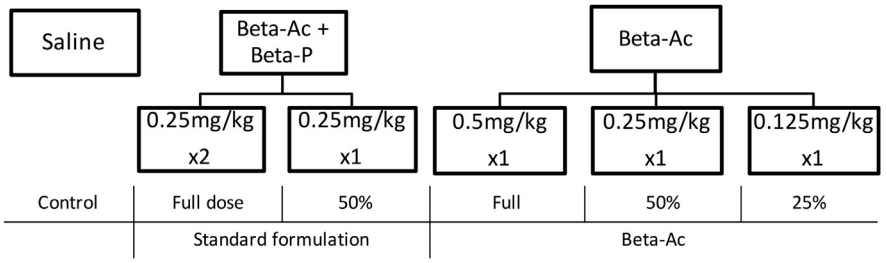
FIGURE 1
Experimental design



Negative control animals were treated with intramuscular saline solution. A group of animals was treated with the clinically used formulation of Betamethasone-acetate + Betamethasone-phosphate as either 2 doses of 0.25 mg/kg 24 hours apart (clinical dose) or a single dose (50% total clinical dose). Another group of animals was treated with Betamethasone-acetate only either with a dose equivalent to the full clinical dose (0.5 mg/kg), 50% of the clinical dose (0.25 mg/kg), or 25% of the clinical dose (0.125 mg/kg).

Beta-Ac+Beta-P, betamethasone-acetate+betamethasone-phosphate.

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fetal lung maturation with a fetal drug level of approximately 2 ng/mL at 24 hours.[9]

The preterm sheep model has been used widely for studies of fetal lung maturation because the fetus can be catheterized, the gestation length is appropriate for testing exposure to delivery intervals relevant to the human, and physiological responses can be evaluated. Using a preterm fetal lamb model, we showed that maternal intramuscular Beta-Ac+Beta-P was more effective than Beta-P alone for improving lung compliance and increased expression of surfactant protein mRNA.[12] Low-dose maternal infusions of Beta-P in catheterized pregnant sheep also increased expression of fetal lung maturation markers, despite much lower fetal maximal concentrations than the Beta-Ac+Beta-P that is used clinically.[13] The pharmacokinetic data suggest that the duration of fetal exposure to a low plasma level of corticosteroids may promote fetal lung maturation better than shorter exposures to the higher plasma concentrations.

Hence, considering the pharmacokinetic profile of Beta-Ac, we hypothesized that a single lower dose of Beta-Ac would promote lung maturation comparable with the standard treatment with lower fetal exposure. Clinical studies of drug and dosage are impractical for either pharmacokinetic or pharmacodynamic assessments of new treatment strategies. Therefore, we tested 3 doses of Beta-Ac that were equivalent to the full, one-half, and one-quarter of the total Beta-Ac+Beta-P dose in preterm fetal and newborn lamb models as an initial strategy to refine a treatment strategy for clinical evaluation.

Methods

Animal studies

The protocols were approved by the animal ethics committee of The University of Western Australia (RA/3/100/1378). We used chronically catheterized pregnant sheep and their fetuses for drug level measurements and separate preterm ventilated lambs to assess fetal lung maturation after maternal ANS treatment. To reduce the risk of preterm labor from ANS, time-mated ewes with singleton fetuses were treated with 1 intramuscular dose of 150-mg medroxyprogesterone acetate (Depo-Provera; Pfizer, New York, NY) at 110 days of gestation for pharmacokinetics studies and at 115 days of gestation for pharmacodynamics studies. No other doses of medroxyprogesterone acetate were given, and we did not administer other tocolytics.

For pharmacodynamics studies, animals were randomized to receive either saline solution (control animals) or 1 of the following treatments: 2 doses of Beta-Ac+Beta-P (Celestone Chronodose; gift from Merck Shar & Dohm Corp., Inc, Kenilworth, NJ) 0.25 mg/kg intramuscularly 24 hours apart, 1 dose of Beta-Ac+Beta-P of 0.25 mg/kg intramuscularly, 1 dose of Beta-Ac 0.5 mg/kg intramuscularly, 1 dose of Beta-Ac 0.25 mg/kg intramuscularly, or 1 dose of Beta-Ac 0.125 mg/kg intramuscularly (Figure 1). The Beta-Ac was a gift from Merck Sharp & Dohme Corp. as a preparation of Beta-Ac that is equivalent to that in Celestone; a 0.25-mg/kg dose approximates the clinical dose of 12 mg of betamethasone for a 50 kg woman and was the same dose used for our previous studies.[9,14]

For delivery, pregnant ewes were anesthetized with intravenous midazolam (0.5 mg/kg) and ketamine (10 mg/kg), followed by spinal anesthesia with 3 mL of 2% (20 mg/mL) lidocaine 48 hours after the first intramuscular treatment injection between 121 and 123 days of gestation. The head of the fetus was exposed through abdominal and uterine incisions; the fetal skin was infiltrated with lidocaine, and a tracheostomy was performed for insertion of an endotracheal tube. After delivery, fetuses were weighted, dried, and placed on a radiant warming bed (Cozy Cot; Fisher & Paykel Healthcare, Auckland, New Zealand) and covered with a plastic wrap for temperature control (Neowrap; Fisher & Paykel Healthcare) for ventilation.

Mechanical ventilation

Mechanical ventilation (Fabian HFO; Accutronic Medical Systems AG, Hirzel, Switzerland) was started immediately with the intermittent positive pressure ventilation mode with standardized settings: initial peak inspiratory pressure (PIP) of 40 cm H_2O, positive end expiratory pressure of 5 cm H_2O, respiratory rate of 50 breaths per minute, inspiratory time of 0.5 seconds, and 100% heated and humidified oxygen. Animals were kept sedated with intramuscular ketamine to avoid spontaneous breathing. We inserted an umbilical artery catheter for blood sampling. Tidal volume (V_t) was measured continuously and kept