OBSTETRICS

The efficacy of antenatal steroid therapy is dependent on the duration of low-concentration fetal exposure: evidence from a sheep model of pregnancy

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BACKGROUND: Antenatal corticosteroids are among the most important and widely used interventions to improve outcomes for preterm infants. Antenatal corticosteroid dosing regimens remain unoptimized and without maternal weight-adjusted dosing. We, and others, have hypothesized that, once a low concentration of maternofetal steroid exposure is achieved and maintained, the duration of the steroid exposure determines treatment efficacy. Using a sheep model of pregnancy, we tested the relationship among steroid dose, duration of exposure, and treatment efficacy.

OBJECTIVE: The study was conducted to investigate the relative importance of duration and magnitude of fetal corticosteroid exposure to mature the preterm fetal ovine lung.

STUDY DESIGN: Ewes with single fetuses at 120 days gestation received an intravenous bolus (loading dose) followed by a maintenance infusion of betamethasone phosphate to target 12-hour fetal plasma betamethasone concentrations of (1) 20 ng/mL, (2) 10 ng/mL, or (3) 2 ng/mL. In a subsequent experiment, fetal plasma betamethasone concentrations were targeted at 2 ng/mL for 26 hours. Negative control animals received sterile saline solution. Positive control animals received 2 intramuscular injections of 0.25 mg/kg Celestone Chronodose (betamethasone phosphate + betamethasone acetate) spaced at 24 hours. Preterm lambs were delivered surgically and ventilated 48 hours after treatment commenced. Maternal and fetal plasma betamethasone concentrations were confirmed by mass spectrometry in a parallel study of chronically catheterized, corticosteroid-treated ewes and fetuses.

RESULTS: The loading and maintenance doses were achieved and maintained the desired fetal plasma betamethasone concentrations of approximately 20, 10, and 2 ng/mL for 12 hours. Compared with the 12-hour infusion-treated animals, lambs from the positive control (2 intramuscular doses of 0.25 mg/kg Celestone Chronodose) group had the greatest functional lung maturation (compliance, gas exchange, arterial pH) and molecular evidence of maturation (glucocorticoid receptor signaling activation), despite having maximum fetal plasma betamethasone concentrations 2.5 times lower than animals in the 20 ng/mL betamethasone infusion group. Lambs from the 12-hour 2-ng/mL betamethasone infusion group had little functional lung maturation. In contrast, lambs from the 26-hour 2-ng/mL betamethasone infusion group had functional lung maturation equivalent to lambs from the positive control group.

CONCLUSION: In preterm lambs that were exposed to antenatal corticosteroids, high maternofetal plasma betamethasone concentrations did not correlate with improved lung maturation. The largest and most consistent improvements in lung maturation were in animals that were exposed to either the clinical course of Celestone Chronodose or a low-dose betamethasone phosphate infusion to achieve a fetal plasma betamethasone concentration of approximately 2 ng/mL for 26 hours. The duration of low-concentration maternofetal steroid exposure, not total dose or peak drug exposure, is a key determinant for antenatal corticosteroids efficacy. These findings underscore the need to develop an optimized steroid dosing regimen that may improve both the efficacy and safety of antenatal corticosteroids therapy.

Key words: betamethasone, dose, fetus, glucocorticoid, lamb, lung maturation, pharmacokinetic, preterm

Antenatal corticosteroids (ANS), in conjunction with advances in obstetric care, neonatal ventilation, and exogenous surfactant therapy, have improved outcomes markedly for preterm infants.[1,2] However, there has been little optimization of ANS therapy for either the total amount of drug given or the dosing protocol.

The first human trial of ANS therapy was reported in 1972 by Liggins and Howie,[3] wherein women in spontaneous preterm labor were assigned randomly to receive either 2 intramuscular injections of 6-mg betamethasone phosphate and 6-mg betamethasone acetate 24 hours apart (approximating the Celestone Chronodose preparation presently in widespread clinical use) or a comparably timed placebo injection of low-activity 6-mg cortisone acetate. The authors reported that, relative to cortisone acetate control, there was a significant reduction in respiratory distress syndrome among babies born 26–32 weeks gestation, who were delivered at least 24 hours after entry to the trial (11.8% in treated babies vs 69.6% in control babies; $P=.02$). A recent Cochrane systematic review of 30 studies (7774 women; 8158 babies) of single-course ANS with either betamethasone or dexamethasone reported significant reductions in key prematurity-associated adverse outcomes, which

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AJOG at a Glance

Why was this study conducted?
The study was conducted to investigate the relative importance of duration and magnitude of fetal corticosteroid exposure to mature the preterm fetal ovine lung.

Key Findings
Once a low concentration (1−4 ng/mL) of fetal plasma betamethasone has been achieved, the duration of this exposure is critical for preterm lung maturation.

What does this add to what is known?
Elevated fetal steroid exposures do not benefit functional maturation of the preterm ovine lung additionally once a low-concentration exposure has been achieved.

included perinatal and neonatal death, respiratory distress syndrome, and intraventricular hemorrhage.[1] Today, ANS dosing remains independent of maternal weight and has not been optimized, which has resulted in significant variation in dosing and the potential for unnecessarily excessive maternofetal steroid exposure.[4,5]

Although the benefits of ANS administration per se are clear, there is also evidence from animal[6-8] and human studies[9-11] of a dose-dependent association between fetal growth restriction and ANS exposure. We and others have suggested that the of maternal dosing, with the use of a standardized lower dose to achieve comparable lung maturation should lower the risk of adverse fetal and newborn infant effects.[12-14] A key requirement to optimize ANS therapy is to define the concentration and duration of maternofetal steroid exposure that is required to mature the preterm lung. Calibration of dose for maternal weight may be 1 means of improving the precision of ANS dosing.

The duration of steroid exposure that is required to mature the preterm lung remains ill-defined. Therefore, the aim of the present study was to evaluate the functional effects of standardized betamethasone infusions on the preterm lung with the use of efficacy and dose confirmation studies.

Methods

Animal work
All animal experiments were performed in Perth (Western Australia) with the approval of the University of Western Australia's Animal Ethics Committee (approval RA/3/100/1378). All dose calculations for infusions were based on ovine betamethasone phosphate pharmacokinetic data.[4] All animals were from the same breeder and were studied during the normal breeding season. One animal from the Celestone Chronodose—positive control group and 1 animal from the 2 ng/mL betamethasone phosphate infusion group (both 12-hour analyses) delivered before 48 hours of treatment and were excluded from analyses.

Experimental design
We performed 3 nested studies: (1) a 12-hour intravenous ANS efficacy study, (2) a 26-hour intravenous ANS efficacy study, and (3) a pharmacokinetic study to confirm dosing delivered in the 12-hour intravenous ANS efficacy study (Figure 1).

For the 12-hour ANS efficacy study, we first used intravenous loading doses and constant infusions of betamethasone phosphate (the soluble component of Celestone Chronodose) to target sustained fetal plasma betamethasone concentrations of either 20, 10, or 2 ng/mL for a period of 12 hours. The ability of these defined exposures to induce fetal lung maturation was compared against animals that received antenatal treatments with either 2 0.25-mg/kg maternal intramuscular injections of Celestone Chronodose (positive control group) spaced by 24 hours or with saline solution (negative control). Lambs were ventilated immediately after delivery for 30 minutes. The following primary physiologic measures were measured at 0, 10, 20, and 30 minutes of ventilation: gas exchange efficacy (lamb arterial pH, pCO2, pO2) and ventilator efficiency (compliance, peak inspiratory pressure).[14,15] The lamb was then killed.

For the 26-hour intravenous ANS efficacy study, we investigated the efficacy of a 26-hour infusion to target a 2-ng/mL betamethasone exposure that was sustained for 26 hours, again compared against positive (Celestone Chronodose) and negative (saline solution) control animals.

For the pharmacokinetic dose confirmation study, chronically catheterized ewes and fetuses were used to confirm the maternofetal betamethasone exposures that were achieved for the 12-hour infusion groups and the positive control group that received the clinical dose of Celestone Chronodose.

Twelve-hour intravenous ANS efficacy study
Fifty-six ewes with single fetuses at 115 days gestational age received an intramuscular injection of 150 mg medroxyprogesterone acetate (Depo-Ralovera; Pfizer, West Ryde, NSW, Australia) to decrease the risk steroid-induced labor and were then randomized to either infusion or intramuscular injection treatment groups.

For infusion-treatments, 36 animals had a brief recovery surgery for placement of a single maternal jugular catheter (7F Multi-Lumen Venous Catheter; Arrow International, Reading, PA)[14] at 120 days gestational age. An ambulatory infusion pump (CADD Solis; Smiths Medical, St Paul, MN) was then secured to each ewe's back. A 4-mg/mL betamethasone preparation (Betnesol; Focus Pharmaceuticals, London, UK) was used for all infusions. Nine animals received a saline solution loading dose and 12-hour saline solution infusion as a negative control. All loading doses were 10 mL and were given over a 30-second period. All infusions were delivered at a rate of 7.5 mL/hr. Animals (n=9/group) received an intravenous loading dose followed by constant infusion of