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Antenatal corticosteroid therapy: Current strategies and identifying mediators and markers for response

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ABSTRACT

Landmark early work has led to the nearly universal use of antenatal corticosteroids to accelerate fetal lung maturity with pregnancies complicated by impending preterm birth. Antenatal corticosteroids clearly reduce respiratory morbidity, death, and other adverse neonatal outcomes. Limited pregnant human pharmacokinetic data and some animal data give clinicians some information as to the behavior of the drug in the body. However, there is controversy about the type, amount, and frequency of steroid to use for this therapy. This review article summarizes the history, clinical use, and pharmacology of antenatal steroids. In addition, the review highlights some potential mediators of steroid response and current research strategies aimed at possible optimization of this therapy.

History and clinical uses of antenatal corticosteroids

Astute observations by New Zealand researchers Liggins and Howie led to one of the most important therapeutic treatments in obstetrics. Noting that prematurely delivered lambs who had received steroid infusions survived better than those that had not, the researchers also found that the lungs of the steroid-treated lambs were partially expanded.[1] This work was confirmed in lambs and rabbits by others.[2,3] This was followed by Liggins and Howie's[4] landmark study in humans confirming the significant decrease in neonatal respiratory distress syndrome (RDS) in infants of women given antenatal corticosteroid (ACS) treatment before preterm delivery. A worldwide wave of trials followed to evaluate this therapy.

The trials were synthesized in a very early Cochrane systematic review written by Crowley. A total of 18 trials, including over 3700 babies, clearly demonstrated that exposure to a single course of ACS was associated with a significant reduction in mortality (odds ratio = 0.60, 95% confidence interval: 0.48–0.75), RDS (odds ratio = 0.53), and intraventricular hemorrhage in preterm infants.[5] In addition, no adverse consequences were identified in the meta-analysis. The updated meta-analysis includes 21 trials (3885 women and 4269 infants).[6] It demonstrates ACS benefit for even more neonatal outcomes including death [relative risk (RR) = 0.69, 95% CI: 0.58–0.81], RDS (RR = 0.66, 95% CI: 0.59–0.73), intracranial hemorrhage (RR = 0.54, 95% CI: 0.43–0.69), and necrotizing enterocolitis (RR = 0.46, 95% CI: 0.29–0.74). These benefits were present across a wide range of preterm gestational ages. Subsequent work has also found that infants born as early as 23 weeks receive a benefit from ACS treatment with 82% reduction in odds of death.[7] Follow-up studies of neurodevelopmental outcomes of children from several trials have failed to find any long-term adverse impacts of the therapy.[8]

For women who deliver more than seven days after a completed course of ACS who have a recurrence of preterm labor, a "rescue" course may be considered.[9] Some trials found

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additional neonatal benefit from this intervention.[10] However, some evidence challenges this notion after finding that most neonatal morbidities were not different if delivery was more than 7 days after ACS treatment compared to within 7 days of ACS treatment.[11] Routine weekly courses of ACS are not recommended due to associations with fetal growth restriction and a potential increased risk of cerebral palsy, although more studies are needed to confirm this association.[9,12–14]

Betamethasone (BMZ) and dexamethasone (DEX) are the most widely studied corticosteroids and have been the preferred treatments to accelerate fetal organ maturation.[9] BMZ is administered as two 12-mg doses given intramuscularly 24 h apart. DEX is administered as four 6-mg doses given intramuscularly 12 h apart. Each drug has been used in different studies in different dose and timing regimens. The commonly used dose, timing, and frequency regimen above was determined empirically and recommended by a NIH consensus panel in 1994.[15] BMZ has been used in more studies than DEX and tends to be favored, at least in the United States.[16] In general, results from trials comparing BMZ to placebo compared to results from DEX versus placebo trials demonstrated greater reduction in morbidities.[16] However, trials of use of postnatal ACS to treat respiratory morbidity have not demonstrated efficacy.[17] Studies investigating ACS outcomes in women with multiple gestations show similar benefits to women with singleton gestations.[18] ACS is used currently in multiple gestations with threatened preterm birth in the same doses as used for singleton pregnancies.

ACS pharmacokinetics and pharmacodynamics

ACS is given as injections to women in threatened preterm labor. BMZ therapy is typically a combination injection of 6 mg of betamethasone acetate and 6 mg of betamethasone sodium phosphate, while DEX contains only 6 mg of dexamethasone phosphate. Betamethasone phosphate and dexamethasone are rapidly absorbed, whereas betamethasone acetate is more slowly absorbed and metabolized, providing for a prolonged effect. Due to fewer injections, betamethasone is often preferred over dexamethasone. BMZ pharmacokinetics is complex due to the mixture of the two salts with different bioavailability. Both are pro-drugs and they will undergo de-acetylation and de-phosphorylation to be converted to the active drug. In sheep, the terminal half-life of BMZ acetate is about 14 h while for BMZ phosphate is approximately 4 h.[19]

In addition, maternal physiologic changes in the renal, gastrointestinal, and cardiovascular system that occur during pregnancy can influence pharmacokinetic parameters.[20] During human pregnancy, cardiac output increases up to 50%.[21] Maternal blood volume expands up to 50%, and glomerular filtration rate increases by 50% as well.[20] These changes occur early in pregnancy and thus are in place at the time when ACS therapy would be utilized. Given these physiologic changes, the measured clearance of betamethasone is higher in pregnancy than in nonpregnant controls.[22] However, since the volume of distribution is also increased, the half-life of the drug remains unchanged.[22]

Ballard's group measured serum concentrations of BMZ in 20 human mothers and 43 premature infants at various times after treatment with betamethasone for RDS prevention.[23] After BMZ administration, maternal serum concentration peaked in 1 h at 75 μg of cortisol equivalents per 100 ml. The concentration of BMZ then was halved by 6 h. To investigate the fetus, BMZ was measured in cord blood. BMZ concentration was 14.3 μg of cortisol equivalents per 100 ml at 1 h. BMZ concentration decrease to a level of 4.7 at 20 h. After the 2nd dose of BMZ, the mean levels were 15.0 μg of cortisol equivalents per 100 ml compared to 12.0 μg per 100 ml for the same period after the 1st dose. BMZ was not detected in cord blood obtained 62 h after the first dose. The Figure displays the concentration–time curves from this study.[23] There is a paucity of pharmacokinetic studies of ACS in pregnant humans.

Further, pharmacokinetic parameters also differ based on body weight. Della Torre's group investigated the effect of body size and multiple gestations on pharmacokinetics parameters in 77 pregnant women.[24] This study compared the pharmacokinetic parameters between singleton ($n = 64$) and twin ($n = 13$) pregnancies and found that the pharmacokinetic parameters were similar between the two groups. They further postulated that no dose adjustment was required for multiple gestations.[24] Pharmacokinetic parameter variability was observed with maternal lean body weight. The study showed that, in addition to gestational age, lean body weight explained nearly 40% of the inter-individual variability on betamethasone volume of distribution at the steady state.[24]

A study comparing oral versus intramuscular BMZ administration found no difference in the frequency of RDS between the two routes of administration. However, the oral dose was associated with increased neonatal morbidity, namely sepsis and intraventricular hemorrhage, and therefore was not recommended.[25] In general, studies of oral administration did not show the benefits of intramuscular administration and thus the intramuscular route is recommended. Intravenous injection of betamethasone has been less frequent in studies and given mostly in studies of HELLP syndrome.[26,27] While usually the exact salt utilized has not been specified, it may only be the phosphate component that would be needed.[16]

Antenatal corticosteroids freely cross the placenta in their biologically active forms. One enzyme that regulates the passage of glucocorticoids in the placenta is 11 beta-hydroxysteroid dehydrogenase type-2.[28] The reduced bioavailability of ACS in the fetal circulation is due to placental metabolism. The maternal vein concentration of betamethasone is approximately 70–75% higher than the fetal venous concentration.[4,23,29]

Studies indicate that BMZ and DEX bind to glucocorticoid receptors (GR) with an affinity more than five times higher than cortisol. Betamethasone provides more than 75% receptor occupancy. Glucocorticoids regulate the expression of glucocorticoid-responsive genes and influence a broad spectrum of physiological processes including inflammation.[30–32] ACS acts in the fetal lung to stimulate the maturation process. This is commonly attributed to architectural and biochemical changes that improve both lung mechanics and