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Title

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Permalink

<https://escholarship.org/uc/item/1n55h24d>

Journal

Pediatric Research, 86(5)

ISSN

0031-3998

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Publication Date

2019-11-01

DOI

10.1038/s41390-019-0538-x

Peer reviewed

Cover Page

Title: Optimizing Antenatal Corticosteroid Therapy for Improving Outcome of Premature Infants

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Author contributions: Both authors drafted and revised the manuscript; both have approved the final version submitted

Financial support: none

Disclosure statement: The authors declare no competing financial interests in relation to the work described.

Category of work: commentary

Bullet points: N/A for a commentary

Antenatal corticosteroid (ACS) therapy for women with anticipated preterm delivery stands as one of the major advances in caring for preterm infants, together with improvements in respiratory support and exogenous surfactant. Following an NIH Consensus Conference in 1994, ACS therapy has become standard of care in many countries and currently is used as an indicator of quality of maternity care in the U.S. Elevated corticosteroid *in utero* hastens development of glucocorticoid-responsive tissues and results in reduced incidence of respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis and death for preterm infants (1). Moreover, with the dosing regimen commonly used (12 mg IM q 24 x 2 of betamethasone phosphate + betamethasone acetate (Celestone Soluspan®)), short-term risks for the mother and infant are minimal. In countries where ACS therapy is available and widely used, a sizeable percentage of pregnant women could potentially receive this therapy for early preterm labor, late preterm labor and elective cesarean section without labor. However, much of the world's population does not have access to the drug and/or appropriate perinatal medical services.

The concept of ACS to enhance fetal maturity began with observations by Liggins in the 1960s (2). Working with a sheep model to investigate mechanisms of parturition, he serendipitously observed that lambs born prematurely after dexamethasone treatment had partial lung inflation. He proposed that corticosteroid exposure had accelerated fetal maturity, including lung development and surfactant production. This seminal observation led to a clinical trial of ACS in women, and the positive results reported in 1972 have been confirmed in numerous subsequent trials (1). Liggins and Howie chose a dose of 12 mg Celestone Soluspan, repeated at 24 hours, with the expectation that rapid hydrolysis of the phosphate form would provide early peak levels of betamethasone and that slower hydrolysis of the acetate form would give sustained exposure (3). This hypothesis was confirmed by measurements of betamethasone in cord blood, with peak levels at ~1 h (20 ng/ml) and a prolonged half-life (~12 h) (4). These plasma

levels of betamethasone, which provide a physiologic stress level of glucocorticoid (4), should provide a near-maximal maturational response in the fetus based on studies of surfactant-related components in cultured human fetal lung (5). Indeed, in a subsequent trial, Liggins found no improved efficacy for preventing RDS using twice the dose of Celestone (24 mg; Liggins, personal communication). However, targeting the lowest efficacious dose should be the goal of any therapy.

Can the dosing regimen for ACS be improved with regard to risk:benefit and individualizing treatment? Certainly, the same dose of ACS is not optimal for women at extremes of body weight, as demonstrated by the pharmacokinetic data of Della Torre (6), and we recommend that dosing be given on a per kg basis as used for many other drugs. Assuming an average maternal weight at 26 weeks gestation of 80 kg as representative of women in published clinical trials of ACS, the recommended dose of Celestone would be 0.15 mg/kg given IM. Complications of pregnancy affecting placental function may alter corticosteroid passage from mother to fetus; however, this possibility needs further study before considering an adjustment to the dose. Other forms of glucocorticoid might provide better pharmacokinetics of fetal exposure; however, hydrocortisone is not preferable, because of high peak levels and fast clearance, increasing risk for off-target effects and un-sustained maturational responses (7).

In this issue of the Journal, Schmidt and colleagues report pharmacokinetics and biologic effects of oral ACS therapy for lung maturation in sheep (8). It is astonishing to realize that, as these authors point out, “despite being used for nearly 50 years, the corticosteroid, dose, treatment interval and route of treatment remain largely unexplored (8).” Thus, although the guiding principle of therapeutics is to give the lowest effective dose, we have yet to determine such a dose for antenatal glucocorticoids. This principle is particularly important for glucocorticoids, which have multiple powerful effects, and even more so when treating the preterm fetus, who normally has a low cortisol concentration (9). Although

antenatal steroids clearly have multiple benefits that outweigh theoretical risks for infants born preterm, data suggest that prenatal exposure may also have long-term effects on infants delivered at term gestation (10-12). Since a large percentage of women given antenatal glucocorticoids do not deliver preterm, it is vital to decrease the exposure of fetuses who do not derive the benefits of ACS on preterm birth but may experience later effects (10).

The authors first investigated physiologic responses and pharmacokinetics of a single 0.33mg/kg dose of oral betamethasone phosphate or dexamethasone phosphate (calculated to compensate for an estimated bioavailability of 80% of the intramuscular dose). A single dose of oral betamethasone phosphate had comparable lung maturational effects to intramuscular Celestone at two days, but had lost efficacy by 5 days, likely due to its shorter half-life compared to betamethasone acetate. However, when two doses of 0.16mg/kg were given 24 hours apart, the pulmonary effects of oral betamethasone were similar to the effects of IM Celestone through the end of the 7-day study period. In addition, this regimen resulted in a lower peak concentration than the single oral dose or the IM dose, thus decreasing fetal exposure to the drug.

In a surprising finding, they discovered that the same dose of dexamethasone resulted in 4-fold lower serum concentrations in both maternal and fetal plasma and had no significant effect on lung maturation. However, based on limited human pharmacokinetic data (4, 13-16), the difference between dexamethasone and betamethasone bioavailability observed in sheep does not occur in humans. In addition, the maternal:fetal distribution is different in sheep than in humans, requiring higher dosing in the sheep. These species differences serve as a reminder of the need to be vigilant regarding the limitations of animal models for human biology. The numerous obstacles to studying corticosteroid pharmacokinetics and biologic effects in pregnant women and fetuses will be difficult to surmount, but it is encouraging that a comparative pharmacokinetic study is underway in women (NCT03668860). The current report provides clear proof of principle

that, in the sheep, oral administration of betamethasone enhances lung maturation. In addition, these results suggest that a lower dose of oral betamethasone or dexamethasone phosphate may provide efficacy comparable to Celestone while decreasing peak fetal exposure for human infants.

Oral dosing of ACS for lung maturation in human newborn infants would be a lower-cost, more easily accessible treatment option, potentially leading to broader global adoption. However, the unexpected increase in infections and neonatal mortality seen in a previous trial of ACS (IM dexamethasone) in low-middle income countries is a reminder that numerous known and unknown factors will influence outcomes in different countries and health care delivery settings (17). Citing a “clear justification for further randomized controlled trials to evaluate the efficacy of ACS in facility settings in lower-income countries,” the World Health Organization established an international research collaboration to undertake two trials of antenatal corticosteroids in pregnancies at risk of preterm delivery, one enrolling women before 34 weeks gestation and the second between 34⁰ and 36⁰ weeks gestation (18).

If proven beneficial through careful clinical trials with comprehensive evaluation, a lower dose and oral administration would be an enormous step toward making “the most effective underutilized treatment available to improve outcomes for fetuses at risk for preterm delivery (8)” more globally available and safer. Ultimately, children and society in general will be best served by improved availability and resources for family planning and perinatal care combined with optimal preventative therapy for improving the outcome of infants born prematurely.

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