Dexamethasone versus betamethasone as an antenatal corticosteroid (ACS)

UN Commission / Born Too soon Care Antenatal Corticosteroids Working Group
August 20, 2013

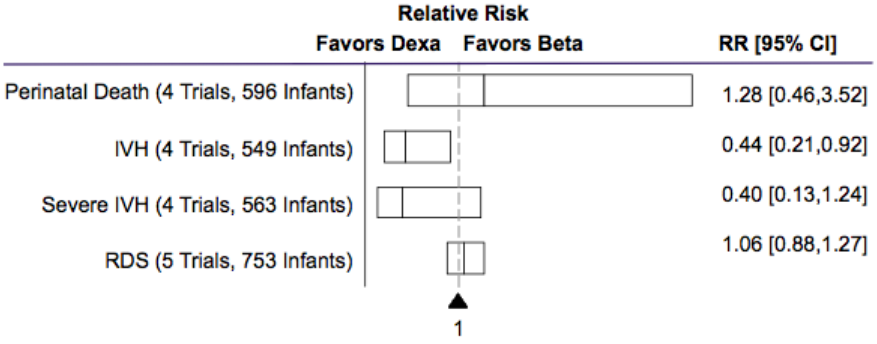
Overview: Dexamethasone and betamethasone are the two antenatal corticosteroids (ACS) recommended for accelerating fetal lung development in threatened preterm birth. The WHO, NIH, ACOG, RCOG, and WAPM list both as effective drugs for preventing complications of prematurity, using either a dosage of 24 mg of dexamethasone (4 doses of 6 mg 12 hours apart) or 24 mg of betamethasone (2 doses of 12 mg 24 hours apart). Historically, these drugs have often been used interchangeably, but betamethasone has sometimes been preferred, as in the current WAPM guideline[1,2].

As of July 2013, the 18th list of WHO Model List of Essential Medicines, which includes ACS for the first time, lists only dexamethasone for fetal indications.[3] The Executive Summary of the WHO Expert Committee explains, "While alternative steroids with similar efficacy were available, dexamethasone was considered the most appropriate product based on availability and cost."[4]

A review of the comparative efficacy, safety, availability, and cost reveals why dexamethasone is often the best choice for expanding the reach of life-saving ACS treatment.

1. Efficacy: Dexamethasone and betamethasone are equally acceptable. Two Cochrane reviews found some better outcomes for each drug, but both concluded further study would be needed to recommend one steroid as superior to the other. A 2006 review of studies comparing ACS to control included 6 trials using dexamethasone and 14 trials using betamethasone. Betamethasone was more effective in reducing RDS (44% vs 20%), while reduction in mortality was similar (33% vs 28%).[5]

A 2008 Cochrane review of 9 studies directly comparing corticosteroids found substantially greater reduction in intraventricular hemorrhage (IVH) for dexamethasone, with no other statistically significant difference in primary outcomes, as shown below (not all studies reported all primary outcomes).[6]



2. Safety: Dexamethasone and betamethasone are both acceptable. The 2006 review showed some elevated risks for the mother from dexamethasone, particularly of puerperal sepsis, with a risk ratio of 1.74 [1.04 to 2.89] compared to 1.00 [0.58 to 1.72] for betamethasone.[7] However, neither review identified any other statistically significant differences in reported adverse effects. Despite potentially increased risk of maternal sepsis and fewer trials for dexamethasone, Cochrane authors were able to conclude that antenatal dexamethasone is an overall safe and effective intervention.

A large trial (A*STEROID) is underway to definitively compare the two drugs, with results expected in 2015.[8] In the meantime, as acknowledged in the WAPM as well as RCOG, ACOG, and NIH guidelines, no definitive evidence supports a clinical preference for either drug based on the balance of efficacy and safety outcomes.

3. Availability: The specific betamethasone used for fetal indications faces major supply shortages, dexamethasone is widely available. Not all injectable betamethasone is equivalent. The recommended formulation for preterm birth is a less available mixture of long-acting betamethasone acetate (beta-ac) and fast-acting betamethasone phosphate (beta-PO_4). This mixture is used in the bulk of betamethasone trials, including 8 of 14 included in the 2006 Cochrane review (one used beta-PO4 only and 5 others used an unspecified formulation). Though generic beta-PO_4 injection is commonly available, data is limited to one trial vs control[2] and one comparative study of 69 infants which produced no statistically significant results.[6] Beta-PO_4 is therefore not recommended for fetal indications.

The betamethasone (beta-ac+beta-PO_4) used in most trials is best-known as Celestone®, with one comparably priced generic identified from American Regent. Celestone has faced shortages in recent years,[9] and manufacture was suspended in 2004,[10] both for reasons not specified by Merck, its manufacturer. American Regent reported "sufficient inventory" as of July 23, 2013.[11] Beta-ac+beta- PO_4 is not sold at all in some countries, including India.

Dexamethasone sodium phosphate, in contrast, is available globally and from suppliers including UNFPA and Mission Pharma[12] among dozens of other vendors.[13] Widespread availability is due in part to its use in many other indications. Dexamethasone sodium phosphate is listed in four other sections of the current WHO EML[3] and on most national essential medicines lists.[14]

4. Cost: A course of dexamethasone is far less expensive than a course of betamethasone
Depending on geography, a full course of dexamethasone may cost around $1 USD, compared to over $35 for a course of betamethasone (Celestone). Accounting for wastage due to non-optimal package size, a course of dexamethasone still costs less than 4% of the cost of a course of betamethasone. While dexamethasone requires four injections compared to two for betamethasone, the cost of syringe, needle, and swab is relatively small at $0.07 USD per injection.[15]

5. Summary: For treatment of women at risk of preterm delivery, dexamethasone is recommended over betamethasone based on its efficacy, safety, wide availability, and low cost. While studies suggest some greater risk of maternal sepsis, dexamethasone is overall a safe drug with better outcomes in reducing IVH and has been found equally acceptable for clinical use. Dexamethasone faces none of the supply problems of betamethasone and is over 20 times cheaper per 24-mg course.

---

[1] WAPM: Guideline for the use of antenatal corticosteroids for fetal maturation (2008)
[2] Cochrane summary: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth
[3] WHO Model List of Essential Medicines, 18th list (April 2013)
[4] Executive summary of the 19th Meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines in Geneva, Switzerland, 8-12 April 2013
[5] Dexamethasone vs betamethasone outcomes:
RDS: RR 0.80, 95% CI 0.68 to 0.93, 6 studies, 1457 infants vs RR 0.56, 95% CI 0.48 to 0.65, 14 studies, 2563 infants
NMR: RR 0.72, 95% CI 0.55 to 0.94, 6 studies, 1468 infants vs RR 0.67, 95% CI 0.54 to 0.82, 12 studies, 2488 infants
[6] Cochrane: Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth
[7] Dexamethasone vs betamethasone outcomes:
Puerperal sepsis: RR 1.74, 95% CI 1.04 to 2.89, 4 studies, 536 women vs RR 1.00, 95% CI 0.58 to 1.72, 4 studies, 467 women
Chorioamnionitis: RR 1.35, 95% CI 0.89 to 2.05, 4 studies, 575 women vs RR 0.71, 95% CI 0.50 to 1.01, 8 studies, 1910 women
[8] Crowther et al. A*STEROID study protocol. BMC Pregnancy and Childbirth 2013 13:104.
[9] American Society of Health-System Pharmacists Celestone Soluspan drug shortage bulletin
[10] FDA docket: Determination That Celestone Soluspan Injection and Celestone Injection Were Not Withdrawn From Sale for Reasons of Safety or Effectiveness
[11] American Regent Products Update – July 23, 2013
[12] International Drug Price Indicator Guide
[13] Proposal for the inclusion of dexamethasone on the WHO EML, Appendix A
[14] Hill S, Yang A, Bero L (2012) Priority Medicines for Maternal and Child Health: A Global Survey of National Essential Medicines Lists. PLoS ONE 7(5): e38055. doi:10.1371/journal.pone.0038055
[15] Proposal for the inclusion of dexamethasone on the WHO EML, Section 12