NIH Consensus Statement

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Antenatal Corticosteroids Revisited: Repeat Courses

NATIONAL INSTITUTES OF HEALTH
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NIH Consensus Development Conferences are convened to evaluate available scientific information and resolve safety and efficacy issues related to a biomedical technology. The resultant NIH Consensus Statements are intended to advance understanding of the technology or issue in question and to be useful to health professionals and the public.

NIH Consensus Statements are prepared by nonadvocate, non-Federal panels of experts, based on (1) presentations by investigators working in areas relevant to the consensus questions during a 2-day public session, (2) questions and statements from conference attendees during open discussion periods that are part of the public session, and (3) closed deliberations by the panel during the remainder of the second day and morning of the third. This statement is an independent report of the consensus panel and is not a policy statement of the NIH or the Federal Government.

Reference Information

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Antenatal Corticosteroids Revisited: Repeat Courses

This statement reflects the panel's assessment of medical knowledge available at the time the statement was written. Thus, it provides a "snapshot in time" of the state of knowledge of the conference topic. When reading the statement, keep in mind that new knowledge is inevitably accumulating through medical research.

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Disclosure Statement

All of the panelists who participated in this conference and contributed to the writing of this consensus statement were identified as having no financial or scientific conflict of interest, and all signed conflict of interest forms attesting to this fact. Unlike the expert speakers who present scientific data at the conference, the individuals invited to participate on NIH consensus panels are selected specifically because they are not professionally identified with advocacy positions with respect to the conference topic or with research that could be used to answer any of the conference questions.

Abstract

Objective

To provide health care providers, patients, and the general public with a responsible assessment of currently available data regarding the benefits and risks of repeat courses of antenatal corticosteroids.

Participants

A non-Federal, non-advocate, 16-member panel representing the fields of obstetrics and gynecology, pediatrics, maternal and fetal medicine, neonatology, medical ethics, community health, pharmacology, psychology, and reproductive biology. In addition, 13 experts in these same fields presented data to the panel and to a conference audience of approximately 200.

Evidence

The literature was searched using MEDLINE and an extensive bibliography of references was provided to the panel. Experts prepared abstracts with relevant citations from the literature. Scientific evidence was given precedence over clinical anecdotal experience.

Consensus Process

The panel, answering predefined questions, developed their conclusions based on the scientific evidence presented in open forum and the scientific literature. The panel composed a draft statement that was read in its entirety and circulated to the experts and the audience for comment. Thereafter, the panel resolved conflicting recommendations and released a revised statement at the end of the conference. The panel finalized the revisions within a few weeks after the conference. The draft statement was made available on the World Wide Web immediately following its release at the conference and was updated with the panel's final revisions.

Conclusions

The collective international data continue to support unequivocally the use and efficacy of a single course of antenatal corticosteroids using the dosage and interval of administration specified in the 1994 Consensus Development Conference report.

The current benefit and risk data are insufficient to support routine use of repeat or rescue courses of antenatal corticosteroids in clinical practice.

Clinical trials are in progress to assess potential benefits and risks of various regimens of repeat courses. Until data establish a favorable benefit-to-risk ratio, repeat courses of antenatal corticosteroids, including rescue therapy, should be reserved for patients enrolled in clinical trials.

Introduction

Preterm delivery remains a major cause of illness and death in infants. Corticosteroid treatment of pregnant women who deliver prematurely was first introduced in 1972 to enhance fetal lung maturity. Subsequent research focused on the ability of corticosteroids to reduce mortality and brain injury in preterm neonates.

In 1994, the National Institutes of Health sponsored a Consensus Development Conference on the Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes to assess the effectiveness of antenatal corticosteroid therapy. The consensus panel concluded that giving a single course of corticosteroids to pregnant women at risk for preterm delivery reduces the risk of death, respiratory distress syndrome, and intraventricular hemorrhage in their preterm infants.

The 1994 panel noted that optimal benefit of antenatal corticosteroid therapy lasts 7 days. The panel also noted that the potential benefits and risks of repeated administration of antenatal corticosteroids 7 days after the initial course are unknown and called for additional research on this issue. However, during recent years the use of repeat courses of antenatal corticosteroids has become widespread in the United States, England, and Australia. Such courses include weekly dosages, occasional dosages, or rescue therapy (single-course steroids) given on an as-needed basis for planned or imminent delivery.

The NIH organized the current conference to present research on repeat courses of antenatal corticosteroid therapy. After a day of presentations and audience discussion, an independent, non-Federal consensus development panel weighed the scientific evidence and wrote a draft statement that was presented to the audience on the second day of the conference.

The consensus statement addressed these three questions:

- Is the evidence on benefits and risks of repeat courses of antenatal corticosteroids sufficient to permit consensus recommendations?
- If so, what are the recommendations?
- If not, what additional information should be obtained?

The primary sponsors of this meeting were the National Institute of Child Health and Human Development and the NIH Office of Medical Applications of Research. The National Institute of Nursing Research and the National Heart, Lung, and Blood Institute were co-sponsors.

Is the Evidence on Benefits and Risks of Repeat Courses of Antenatal Corticosteroids Sufficient to Permit Consensus Recommendations?

Studies of single versus repeat courses of antenatal corticosteroids were evaluated for benefits and risks through a review of published literature and data presented during the consensus conference.

Benefits

In preterm animals, multiple doses of antenatal corticosteroids improve lung function when compared with a single dose. These benefits include improved lung mechanics and gas exchange as well as increased lung volume and surfactant pools.

No published data on any of the possible benefits to humans of repeat courses of antenatal corticosteroids were available from randomized controlled trials, and the data from nonrandomized controlled trials were limited in quality. Many studies were published as abstracts. The most common research design was a retrospective evaluation of clinical data; other studies were retrospective cohort comparisons. Methodologic inconsistencies, such as variation in latent period from last dose to delivery, in number of repeat courses compared, and variability of inclusion of multifetal pregnancies made it difficult to combine data from multiple studies. Despite their limitations, these studies suggested possible benefits in reduction of the incidence and severity of respiratory distress syndrome, and reduction in the incidence of patent ductus arteriosus. There is little or no evidence to support other possible benefits, including a reduction in mortality rate or reductions in the incidence of intraventricular hemorrhage, chronic lung disease, sepsis, necrotizing enterocolitis, or retinopathy of prematurity.

Risks

Data from studies on both animals and humans raise questions about the safety of repeat doses of antenatal corticosteroids. Animal studies have shown that repeat courses of antenatal corticosteroids have deleterious effects on lung growth and organization, cerebral myelination, the function of the hypothalamic-pituitary-adrenal axis, and retinal development. In addition, there is evidence for a dose dependent effect on fetal growth and persistence of immature lung architecture.

Evidence from human studies on both the short and long-term adverse effects of repeat doses of corticosteroids is contradictory and therefore inconclusive. The available human data come from inadequately controlled observational and retrospective studies, some of which suggest adverse maternal and fetal effects. Even when studies suggest a deleterious outcome, they are generally inconsistent. In addition, none of the studies controlled for postnatal corticosteroid treatment, used widely at the time of the reports available to the panel. The study populations often excluded children whose mothers had received repeat courses of corticosteroids and who delivered late in the preterm period or at term.

Nevertheless, some studies suggest matters of concern. For the mother, these include increased maternal infection and suppression of the maternal hypothalamic-pituitary-adrenal axis. Fetal/neonatal effects include decreased somatic and brain growth, adrenal suppression, neonatal sepsis, chronic lung disease, and mortality. No consistent effect on intraventricular hemorrhage was apparent from the available data. Although no increase in the incidence of cerebral palsy was noted, neurodevelopmental followup studies suggest an increase in psychomotor delay and

behavioral problems. Concern about the effects of repeated corticosteroids on the central nervous system is heightened by the fact that randomized controlled trials of postnatal corticosteroids have found adverse neurologic effects in infants of gestational age similar to those treated in utero.

Summary

Data from currently available studies assessing benefits and risks are inadequate to argue for or against the use of repeat or rescue courses of antenatal corticosteroids for fetal maturation.

If So, What Are the Recommendations?

Clinical Recommendations

- All pregnant women between 24 and 34 weeks gestation who are at risk of preterm delivery within 7 days should be considered candidates for antenatal treatment with a single course of corticosteroids.
- Treatment consists of two doses of 12 mg of betamethasone given intramuscularly 24 hours apart or four doses of 6 mg of dexamethasone given intramuscularly 12 hours apart, as recommended by the consensus panel in 1994. There is no proof of efficacy for any other regimen.
- Because of insufficient scientific data from randomized clinical trials regarding efficacy and safety, repeat courses of corticosteroids should not be used routinely. In general, it should be reserved for patients enrolled in randomized controlled trials. Several randomized trials are in progress.

If Not, What Additional Information Should Be Obtained?

The following research is recommended:

- Well-designed randomized clinical trials which are of sufficient power to evaluate efficacy and safety are needed.
- In light of the possible risks, the design of randomized clinical trials should minimize the exposure of mothers and fetuses while protecting the integrity of the research design.

These trials should assess:

- Clinically important neonatal morbidities, such as respiratory distress syndrome, chronic lung disease, and brain injury.
- Clinically important maternal morbidities, such as infection and adrenal suppression.
- The effects of repeat courses of corticosteroids on patterns of fetal and postnatal growth.
- The potential effects of incremental courses on benefits and risks, since the benefits of repeat courses of antenatal corticosteroids are likely to decrease with advancing gestational age.
- The efficacy and safety of rescue therapy.
- The interaction of repeat courses of antenatal corticosteroids with postnatal corticosteroid therapy.
- Long-term growth and neuropsychological outcome up to at least school age, using state-of-the-art techniques.

In addition:

- Animal studies should evaluate the pathophysiologic and metabolic mechanisms of potential benefits and risks, including the effects of repeat corticosteroids on central nervous system myelination and brain development.

Conclusions

- The collective international data continue to support unequivocally the use and efficacy of a single course of antenatal corticosteroids using the dosage and interval of administration specified in the 1994 Consensus Development Conference report.
- The current benefit and risk data are insufficient to support routine use of repeat or rescue courses of antenatal corticosteroids in clinical practice.
- Clinical trials are in progress to assess potential benefits and risks of various regimens of repeat courses. Until data establish a favorable benefit-to-risk ratio, repeat courses of antenatal corticosteroids, including rescue therapy, should be reserved for patients enrolled in clinical trials.

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