Dexamethasone Therapy for Bacterial Meningitis in Infants and Children

BACKGROUND

Bacterial meningitis affects an estimated 15,000 infants and children in the United States each year. The case-fatality rates for these patients are from 5% to 10%; as many as 20% to 30% of survivors have long-term sequelae, the most common of which is hearing impairment. The reported incidence of hearing loss after meningitis has ranged from 5% to 20% of patients, depending on the selection of patients, techniques used to assess hearing, and etiology. In 1972 to 1977, Dodge and co-workers documented hearing loss in 31% of patients with *Streptococcus pneumoniae* meningitis, 10% with *Neisseria meningitidis* meningitis, and 6% with *Haemophilus influenzae* meningitis. Bilateral sensorineural hearing impairment occurred in 14%, 10%, and 3%, respectively. Newer antimicrobial agents with superior bactericidal activity in cerebrospinal fluid have not reduced morbidity and case-fatality rates compared with conventional therapy.

The pathophysiologic events believed to contribute to adverse outcome from bacterial meningitis include alteration of cerebral capillary endothelial cells that comprise the blood-brain barrier, cytotoxic and vasogenic cerebral edema, and increased intracranial pressure. These events can lead to decreased cerebral perfusion pressure with a resultant diminution in cerebral blood flow causing regional hypoxia and focal ischemia of brain tissue. Because of its anti-inflammatory effects, corticosteroid therapy has been evaluated in experimental meningitis and in infants and children with meningitis. Dexamethasone produced significant reductions in intracranial pressure, brain edema, and lactate concentrations in cerebrospinal fluid in experimental *H influenzae* and *S pneumoniae* meningitis. In addition, the administration of dexamethasone was associated with decreased concentrations of prostaglandin E2 in cerebrospinal fluid and lowered mortality and clinically evident neurologic sequelae in rabbits with experimental pneumococcal meningitis. In experimental *H influenzae* meningitis, dexamethasone given concurrently with antimicrobial therapy significantly reduced spinal fluid concentrations of cachectin (tumor necrosis factor), a cytokine that is believed to participate in the host's inflammatory response. By contrast, a study in rats suggested that corticosteroids can potentiate ischemic injury to neurons. Current information on the pathophysiology of bacterial meningitis in children was recently reviewed, and additional studies are needed.

The results of two placebo-controlled trials of corticosteroid therapy in children with meningitis were published in 1969. Methylprednisolone was used in one study and dexamethasone in the other. In neither study was hearing specifically evaluated in all patients. The investigators in both studies concluded that there were no significant beneficial or adverse effects of corticosteroid therapy. In the study by Belsey et al patients who received dexamethasone, in approximately one third the dose used in the more recent trials, had significantly fewer neurologic complications during hospitalization and at discharge than placebo-treated patients. This effect, however, was discounted because patients in the placebo group were thought to have more serious illness at the time of admission to the hospital. In the study by de Lemos and Haggerty using 40 mg of methylprednisolone,
long-term sequelae occurred more frequently in steroid-treated children than in placebo-treated children.

The results of two double-blind, placebo-controlled trials of dexamethasone therapy for bacterial meningitis in 200 infants and children 2 months of age and older were published recently. Dexamethasone, 0.6 mg/kg/day in four divided doses, or placebo were administered intravenously for the first 4 days of antibiotic therapy, which consisted of cefuroxime (first study) or ceftriaxone (second study). Dexamethasone-treated patients became afibrile earlier than did placebo-treated patients (1.6 vs 5.0 days; *P* < .001). The mean increase in glucose concentration (36.0 vs 6.9 mg/dL; *P* < .001) and decrease in lactate concentration (38.3 vs 19.8 mg/dL; *P* < .005) in cerebrospinal fluid after 24 hours of therapy were significantly greater for dexamethasone-treated patients than for placebo-treated patients.

Dexamethasone-treated children in those two studies were significantly less likely to have moderate or more severe bilateral sensorineural hearing loss (3 of 92, 3.3%, vs 13 of 84, 15.5%; *P* < .01) and to require hearing aids (1 of 92, 1.1%, vs 12 of 84, 14.3%; *P* < .001) when evaluated 3 to 12 months after the illness. The relative risk (95% confidence interval) for developing moderate or greater hearing impairment in placebo-treated patients was 2.54 (1.1 to 5.9) compared to dexamethasone-treated patients using a stratified analysis (Mantel-Haenszel method) of the data from the first and second study considered separately. The relative risk for the combined data was 4.75 (1.6 to 14.1). The relative risks of requiring hearing aids after meningitis were 3.8 (1.4 to 10.3) for separate data and 13.14 (2.9 to 59.7) for combined. One year after illness, neurologic sequelae other than sensorineural hearing loss were found in 3 (4%) of 81 patients given dexamethasone and 9 (12%) of 75 patients given placebo (*P* = .052).

The same investigators have recently completed a third double-blind placebo-controlled study of dexamethasone therapy in 60 patients who received cefuroxime therapy. The data from that study support the findings from the first two trials. For the 260 infants and children enrolled in the three studies, seizures that occurred after admission to the hospital (10 of 133, 7.5%, vs 21 of 127, 16.5%; *P* = .025) and hemiparesis evident at the time of discharge (3 of 133, 2.3%, vs 11 of 127, 8.7%; *P* = .022) occurred significantly less frequently in dexamethasone recipients than in placebo recipients. Bilateral moderate or more severe hearing loss occurred in 15 (13%) of 113 placebo-treated patients and 4 (3%) of 122 dexamethasone-treated patients (*P* < .005) who had been followed up for 3 to 12 months after illness. The relative risk of developing moderate or greater hearing impairment was 4.1 (1.3 to 12.2) for placebo-treated vs dexamethasone-treated children. Because approximately 75% of the study patients had *H influenzae* meningitis, the beneficial effect of dexamethasone on hearing could be determined only in those patients. Too few patients with pneumococcal or meningococcal meningitis were examined to determine the effect of steroid therapy on outcome.

The effect of dexamethasone in lowering the risk of hearing loss appears to be greater in those with milder illness. To determine whether severity of disease influenced outcome, data from 199 patients with *H influenzae* meningitis were analyzed. When the Herson and Todd prognostic score was ≤2.5, indicating a milder illness, the rates of moderate or greater hearing loss in one or both ears (7 of 79, 9%, vs 12 of 56, 21%; *P* = 0.039) and in both ears only (1 of 79, 1%, vs 9 of 56, 16%; *P* = 0.001) were significantly smaller in dexamethasone-treated patients than placebo-treated patients. There was no difference in hearing outcome for the two treatment groups when the Herson-Todd score was >2.5.

Recently, Schaad et al reported a comparative study of ceftriaxone and cefuroxime in the treatment of meningitis. Of interest was the delayed sterilization of spinal fluid seen in the cefuroxime group and the high rate of hearing loss (17%) in that group. On the other hand, only 4% of the ceftriaxone group showed hearing loss at follow-up.

A recent meta-analysis of all trials of steroids in *H influenzae* meningitis concluded that dexamethasone probably reduced the risk of hearing loss.

**ADVERSE EFFECTS**

Dexamethasone therapy was not associated with delayed sterilization of cerebrospinal fluid cultures. Relapse of meningitis occurred in only one patient, a dexamethasone-treated child who had *H influenzae* meningitis. The rate of relapse of *H influenzae* meningitis (1 of 104 steroid-treated patients, 0.96%) was similar to the 0.8% relapse rate observed in 708 patients with *H influenzae* meningitis treated in Dallas from 1969 to 1980 before initiation of those three dexamethasone studies.

Two patients treated with dexamethasone and ceftriaxone developed gastrointestinal bleeding requiring blood transfusions on the second and third days of steroid treatment. It is uncertain, however, whether the bleeding was a result of dexamethasone therapy. Secondary, low-grade fever occurred 24 to 48 hours after stopping dexamethasone in approx-
approximately two thirds of patients. Fever persisted for 24 to 36 hours. No other adverse effects were observed in the 133 patients who received dexamethasone.

RECOMMENDATIONS

1) Dexamethasone therapy probably reduces the likelihood of deafness after H influenzae meningitis, although additional placebo-controlled studies are required before the Committee can make unqualified recommendations. At this stage we recommend individual consideration of dexamethasone for bacterial meningitis in infants and children 2 months of age and older after the physician has weighed the benefits and possible risks. However, the Committee recognizes that some experts have decided not to use dexamethasone therapy until additional data are available. 2) The regimen used in the published studies was 0.6 mg/kg/day in four divided doses given intravenously for the first 4 days of antibiotic treatment. Insufficient data exist to recommend other dosage schedules of dexamethasone or other steroid preparations for therapy of meningitis. 3) If dexamethasone is used it should be administered at the time of the first dose of antibacterial therapy; the effect of dexamethasone therapy when administered more than several hours after the start of parenterally administered antimicrobial therapy has not been determined. 4) In the published11,12 and current clinical trials of dexamethasone therapy, ceftriaxone, cefotaxime, and cefuroxime have been used for antimicrobial treatment. Because of delayed sterilization of cerebrospinal fluid cultures in some infants with H influenzae meningitis and of a greater potential for hearing abnormality in cefuroxime-treated patients,22 the committee does not recommend cefuroxime for therapy of bacterial meningitis. There is no a priori reason to believe that dexamethasone would not be comparably beneficial when administered with other effective antimicrobial regimens such as ampicillin and chloramphenicol. 5) It should be emphasized that dexamethasone therapy should only be considered when the diagnosis of bacterial meningitis has been proved or is strongly suspected on the basis of the cerebrospinal fluid examination, Gram stained smear, or antigen test results. 6) The utility of dexamethasone in treatment of pneumococcal or meningococcal meningitis is not yet known. 7) Dexamethasone should not be used for suspected or proved aseptic or nonbacterial meningitis. If the drug had been started before the diagnosis of nonbacterial meningitis, it should be discontinued when a diagnosis of bacterial meningitis becomes unlikely. 8) “Partially treated” meningitis with negative cultures is also not an indication for continued dexamethasone therapy. 9) The results to date suggest that dexamethasone is effective in those with milder illness; thus, if dexamethasone is used, all patients should be treated, not just those with severe disease. 10) No data are currently available on which to recommend the use of dexamethasone for treatment of bacterial meningitis in infants younger than 2 months of age or of meningitis in those with congenital or acquired abnormalities of the central nervous system, with or without placement of a prosthetic device. 11) Measurements of hemoglobin concentrations and examinations of stool for occult blood should be performed regularly during dexamethasone therapy. If melena or gross blood is observed, dexamethasone therapy should be stopped and the patient should be observed closely for possible transfusion therapy.

These recommendations and warnings may be modified as the results of additional studies become available.
REFERENCES

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