Archives of Disease in Childhood 1992; **67**: 1398–1401

CURRENT TOPIC

Should we use dexamethasone in meningitis?

The Meningitis Working Party* of the British Paediatric Immunology and Infectious Diseases Group

Meningitis in Britain is still a common and serious disease. Each year 2000 cases are reported to the Communicable Disease Surveillance Centre (CDSC), and possibly as many again go unreported. Altogether 70% of cases are in children, and the overall mortality is 10%.[1] This means that more children die each year of meningitis than of either liver disease or kidney disease.[2]

Although the prognosis following bacterial meningitis improved dramatically after the introduction of antibiotics, there has been no major decline in the morbidity or mortality for three decades. This is despite a range of excellent antibiotics which are very effective in destroying the causative organisms. Meningitis is the commonest cause of acquired postnatal sensorineural deafness in childhood,[3] and also produces epilepsy and neurological damage as sequelae.[4 5]

In the past decade evidence has accumulated from both cellular and animal studies to suggest that much of the cerebral damage is the direct result of activation of host inflammatory pathways rather than a direct consequence of the invading organism.[6] Steroids in vitro block the release of inflammatory cytokines from macrophages and other host cells,[7 8] and in vivo animal experiments have shown that both the inflammatory response and the resulting organ damage occurring in meningitis can be reduced by steroids.[9] This has led to the suggestion that anti-inflammatory treatment may be helpful in human disease. A number of clinical trials have now been undertaken which suggest a beneficial effect from steroids, and a heated debate has developed as to whether steroids should now become a routine part of the treatment of meningitis.

How strong is the evidence?

In vitro studies

There is now good evidence that the inflammatory cascade induced by bacterial products such as endotoxin is initiated by cytokines, particularly tumour necrosis factor-α (TNF-α)[10] and interleukin-1β (IL-1β).[11] Synthesis and release of these cytokines can be suppressed by pretreatment of cultured cells in vitro with dexamethasone.[7 8]

Animal studies

The inflammatory response occurring in the cerebrospinal fluid of rabbits after intracisternal injection of either bacterial products such as endotoxin or of live *Haemophilus influenzae* organisms can be blocked by dexamethasone. This is effective when administered before or with (but not after) an antibiotic.[9] TNF-α and 1L-1β concentrations in the cerebrospinal fluid are reduced concomitantly. Similar effects have been shown in experimental pneumococcal meningitis,[12] in which intracranial hypertension, brain water, and cerebrospinal fluid lactate concentrations can be reduced by steroids. In addition, the inflammatory response induced by intracisternal administration of recombinant TNF-α or IL-1β to rabbits is similarly decreased by prior treatment with dexamethasone.[13]

Clinical studies

HAEMOPHILUS INFLUENZAE

Based on this and other evidence, several clinical trials were established, initially by workers in Dallas, studying bacterial meningitis in infants and children. Lebel *et al* studied 200 children on two antibiotic regimens for bacterial meningitis.[14] Most had infection with *H influenzae*. They were randomised to receive either dexamethasone 0·15 mg/kg or placebo at the onset of treatment and then six hourly for four days. These trials suggested that the children treated with steroids had a more rapid correction of abnormal cerebrospinal fluid parameters (glucose, lactate, protein), a shorter duration of fever, and significantly less long term hearing loss than the placebo group. Particularly impressive was the reduction in sensorineural deafness (3·3% in the steroid treated group compared with 15·5% in the placebo group). Critics were quick to point out that the overall death rate in this study was very low (only one patient died) and that the 15·5% incidence of sensorineural hearing loss in the control group was much higher than that found in other studies. (Pomeroy *et al* found an overall incidence of sensorineural hearing loss of 10% in their patients,[15] and other groups have found the incidence to be even lower.) Despite these criticisms, the improvement in morbidity appeared striking.

A further study from the same centre on only 60 patients failed to detect a statistically significant difference between steroid treated and control groups with regard to hearing loss,

Correspondence to:
Dr M J Tarlow,
Department of Paediatrics,
East Birmingham Hospital,
Bordesley Green East,
Birmingham B9 5ST.

*Members include Dr E G Davies (London), Dr D Gibb (London), Dr S Kroll (Oxford), Professor M Levin (London), Dr P Rudd (Bath), Dr M J Tarlow (Birmingham), and Dr A Thomson (Crewe).

although the steroid treated group again showed more rapid normalisation of cerebrospinal fluid abnormalities.[16] Since then, Odio, from Puerto Rico working in conjunction with the Dallas group, again failed to find a statistically significant reduction in deafness in her steroid treated group,[17] but showed an overall reduction in the incidence of 'neurological complications' compared with a placebo group.

Eighteen months ago, a meta-analysis of all published trials of steroids in bacterial meningitis was performed.[18] The results showed that steroids had not reduced the overall risk of death or neurological abnormality at hospital discharge or follow up examination. When many of the variables between studies were eliminated by analysing the only five studies performed primarily in children, there was still no significant difference in this subset. However, restricting the analysis to the three (then) most recent studies, all of which came from the same unit in Dallas, evidence was found that *in haemophilus infections alone*, dexamethasone reduced the risk of bilateral moderate or more severe hearing loss (although a statistically significant benefit was only found in one of these three studies).

Can we apply these results to British practice directly?

The vast majority of cases of childhood meningitis seen in North America in the 1980s were due to *H influenzae*, and the above trials concentrated on this organism. Since these studies, effective haemophilus vaccines have been introduced in many countries, including the USA, and will be in general use in Britain by the end of 1992. Haemophilus meningitis is likely to become much less common in this country within a few years.

So what about the other organisms?

MENINGOCOCCUS

Meningococcal meningitis is at least as common as haemophilus in Europe, and will become relatively more important with the decline of haemophilus disease. However, few data are available for the effect of steroids in this condition.

In a controlled trial of steroids Girgis *et al* studied 429 adults and children with bacterial meningitis in Cairo, Egypt.[19] Of these 267 were due to meningococcal infection. Despite this large number there was no evidence that the steroid treated group fared any better than those given antibiotics alone. The mortality and incidence of serious sequelae was equal in both groups. The authors suggested that this may have been because the damage had already occurred before the patient reached hospital. There is some experimental and clinical support for the suggestion that hearing loss (for example) occurs very early in bacterial meningitis.[20 21] Unfortunately it is difficult to extrapolate from the results of this trial to our own clinical management. These Egyptian patients were extremely sick (60% were comatose on admission), and neither the occurrence of subtle neurological defects nor the incidence of possible side effects was carefully monitored. In addition the pathophysiological changes in meningococcal meningitis may not be identical to those in haemophilus meningitis. The clinical picture differs (meningococcal disease is more frequently associated with septicaemia and a purpuric rash for example), and other as yet undefined factors may have a role in meningococcal disease.

There is no evidence available to assess the role of steroids in meningococcal meningitis with septicaemia and septic shock. In other forms of septic shock there is little evidence that steroids are beneficial (even when given early), and they may possibly be harmful.[22] We would therefore recommend caution in using steroids in children with meningococcal meningitis with associated septic shock until more evidence is available.

PNEUMOCOCCUS

What about pneumococcal meningitis? Although in Britain this is the least common of the three major agents causing bacterial meningitis in infants and children, the morbidity and mortality is higher than for either haemophilus or meningococcal infections. There is little published evidence that steroids may be of value here: the Egyptian study by Girgis and colleagues quoted above found a reduction in the mortality and morbidity of patients with pneumococcal meningitis receiving steroids,[19] and a small retrospective study from Dallas suggested that fewer steroid treated patients had an adverse neurological outcome.[23]

Several other studies have been initiated since 1989, both in North America and in Europe; to our knowledge none of these have yet produced statistically significant results. No evidence is currently available for a role for steroids in neonatal meningitis, although trials are in progress.

Complications of steroids

Do the complications of steroid treatment outweigh its advantages?

Two patients who received steroids in the original Dallas studies had sufficiently severe gastrointestinal bleeding to need transfusion, and two other children had detectable 'occult blood' in their stools.[14] Information on the complications of steroids from many of the other published studies are incomplete, and the overall morbidity of adjunct steroid treatment is, in our opinion, still unclear. An experimental study in rats has suggested that steroids potentiate ischaemic damage to neurons,[24] with obvious implications for clinical management.

The use of dexamethasone may delay sterilisation of the cerebrospinal fluid. Although this was noted in only one patient in the Dallas studies, it remains a clinical concern for many, and further data from other centres would be reassuring.

As all the evidence suggests that steroid treatment is only beneficial if given very early (preferably even before the antibiotic) a number of children with viral meningitis will be treated with steroids for short periods (probably up to 48 hours). No adverse effects from the steroid

treatment have yet been reported, but very few children in this group have been studied, and more information is still required.

Rationale for steroid treatment

The rationale for steroid treatment is dependent on the concept that the damage is primarily due to the host inflammatory response rather than the direct effect of a toxin produced by the organism itself. Is this necessarily the case? There is evidence that it is true in *H influenzae* meningitis,[25] in which the pathogenic material is considered to be lipopolysaccharide of the outer cell membrane (LPS, endotoxin), a substance that primarily provokes the release of host cytokines but is itself largely non-toxic to many mammalian cells. In pneumococcal meningitis, cell wall lipoteichoic acid may play the same part as Gram negative LPS,[26] but here there is some evidence that other substances such as pneumolysin (a pneumococcal exotoxin) may also be involved. Pneumolysin can directly damage tissues, probably by producing pores in cell membranes.[27] If this is part of the mechanism of pneumococcal damage, pneumococcal disease might not be as steroid responsive as haemophilus meningitis. Few studies have been performed on the mechanism of tissue damage in meningococcal meningitis. Although meningococcus, like haemophilus, is a Gram negative organism containing LPS in its outer cell membrane, there is no certainty that it produces tissue damage in the same way; indeed the very different clinical patterns of disease produced by the two organisms suggest that their mechanisms of toxicity may differ in important ways.

There is thus little adequate data from any North American study to demonstrate a convincing benefit resulting from dexamethasone administration in meningitis due to any organism other than haemophilus. More studies are called for. There are still no published studies from Europe, where the incidence of deafness and other complications may be less than in the populations studied by the Dallas group, and where antibiotic use and clinical practice is often different.

After reviewing the evidence, the Committee on Infectious Diseases of the American Academy of Pediatrics concluded that 'Dexamethasone therapy probably reduces the likelihood of deafness after *H influenzae* meningitis . . . The utility of dexamethasone in treatment of pneumococcal or meningoccal meningitis is not yet known'.[28]

Conclusion

In conclusion then, it seems probable that children with haemophilus meningitis may benefit from the use of early adjunct treatment with dexamethasone, particularly in the reduction of deafness. Almost all the evidence for this comes from a single unit in North America, and different parameters have shown benefit in different trials. The advantages of steroid treatment here probably outweigh the disadvantages. The case for pneumococcal meningitis is minimal, based in a retrospective study from Dallas and on a subgroup of a Cairo study performed in a mixed group of adults and children. Very limited information is available for meningococcal meningitis. What evidence there is suggests steroids may not help. As there are well established risks associated with steroid administration to septic patients, especially those in shock, there is an urgent need for further studies to confirm or refute this potentially major change in our management of a widely and justly feared infection.

How easy would these be?

It would be necessary to recruit very large numbers of patients and controls (many hundreds) into a placebo controlled trial of dexamethasone designed to confirm or refute a 50% reduction of moderate/severe deafness in bacterial meningitis. The patients would need careful monitoring and audiological follow up over a prolonged period. We may be approaching the point at which this type of controlled study can no longer easily be performed in Britain alone.

A European multicentre trial may be the answer.

1 Public Health Laboratory Service. *Communicable disease report. Quarterly and annual tabulations 1987*. London: PHLS Surveillance Centre, 1991:13–4.
2 Office of Population Censuses and Surveys. *Mortality statistics, 1988*. London: HMSO, 1990.
3 Fraser GR. Deafness acquired in infancy and childhood. *The causes of profound deafness in childhood*. London: Ballière Tindall, 1976:268–80.
4 Pomeroy SL, Holmes SJ, Dodge PR, Feigin RD. Seizures and other neurological sequelae of bacterial meningitis in children. *N Engl J Med* 1991;**323**:1651–7.
5 Taylor HT, Mills EL, Ciampi A, *et al*. The sequelae of *Haemophilus influenzae* meningitis in school age children. *N Engl J Med* 1991;**323**:1657–63.
6 Saez-Llorens X, Ramilo O, Mustafa MM, Mertsola J, McCracken GH Jr. Molecular pathophysiology of bacterial meningitis: current concepts and therapeutic implications. *J Pediatr* 1990;**116**:671–84.
7 Lee SW, Tsou AP, Chan H, *et al*. Glucocorticoids selectively inhibit the transcription of the interleukin-1β gene and decrease the stability of interleukin-1β mRNA. *Proc Natl Acad Sci USA* 1988;**85**:1204–8.
8 Velasco S, Tarlow M, Olsen K, Shay JW, McCracken GH Jr, Nisen PD. Temperature dependent modulation of LPS-induced IL-1β and TNFα expression in cultured human astroglial cells by dexamethasone and indomethacin. *J Clin Invest* 1991;**87**:1674–80.
9 Mustafa MM, Ramilo O, Mertsola J, Hansen EJ, Beutler B, McCracken GH Jr. Modulation of inflammation and cachectin activity in relation to treatment of experimental *Haemophilus influenzae* type b meningitis. *J Infect Dis* 1989; **160**:818–25.
10 Tracey KJ, Vlassara H, Cerami A. Cachectin/tumour necrosis factor. *Lancet* 1989;**i**:1122–5.
11 Dinarello CA. Interleukin-1. *Rev Infect Dis* 1984;**6**:51–95.
12 Tauber MG, Khayam-Bashi H, Sande MA. Effects of ampicillin and corticosteroids on brain water content, cerebrospinal fluid pressure and cerebrospinal fluid lactate levels in experimental pneumococcal meningitis. *J Infect Dis* 1985;**151**:528–33.
13 Ramilo O, Saez-Llorens X, Mertsola J, *et al*. Tumor necrosis factor-α/cachectin and interleukin-1β initiate meningeal inflammation. *J Exp Med* 1990;**172**:497–507.
14 Lebel MH, Freij BJ, Syrogiannopoulos GA, *et al*. Dexamethasone therapy for bacterial meningitis. Results of two double blind controlled trials. *N Engl J Med* 1988;**319**: 964–71.
15 Pomeroy SL, Holmes SJ, Dodge PR, Feigin RD. Seizures and other neurological sequelae of bacterial meningitis in children. *N Engl J Med* 1990;**323**:1651–7.
16 Lebel MH, Hoyt J, Waagner DC, Rollins NK, Finitzo T, McCracken GH Jr. Magnetic resonance imaging and dexamethasone therapy for bacterial meningitis. *Am J Dis Child* 1989;**143**:301–6.
17 Odio CM, Faingezicht I, Paris M, *et al*. The beneficial effects of early dexamethasone administration in infants and children with bacterial meningitis. *N Engl J Med* 1991;**324**: 1525–31.
18 Havens PL, Wendelberger KJ, Hoffman GM, Lee MB, Chusid MJ. Corticosteroids as adjunctive therapy in bacterial meningitis. A meta-analysis of clinical trials. *Am J Dis Child* 1989;**143**:1051–5.

19 Girgis NI, Farid Z, Mikhail IA, Farrag I, Sultan Y, Kilpatrick ME. Dexamethasone treatment for bacterial meningitis in children and adults. *Pediatr Infect Dis J* 1989;**8**:848–51.
20 Bhatt S, Halpin C, Wen Hsu, *et al*. Hearing loss and pneumococcal meningitis: an animal model. *Laryngoscope* 1991;**101**:1285–92.
21 Vienny H, Despland PA, Lutschg J, *et al*. Early diagnosis and evolution of deafness in childhood bacterial meningitis: a study using brainstem auditory evoked potentials. *Pediatrics* 1984;**73**:579–86.
22 Bone RC, Fisher CJ, Clemmer TP, Slotman GJ, Metz CA, Balk RA, and the methylprednisolone severe sepsis study group. A controlled clinical trial of high dose methyl prednisolone in the treatment of severe sepsis and septic shock. *N Engl J Med* 1987;**317**:653–8.
23 Kennedy WA, Hoyt MJ, McCracken GH Jr. The role of corticosteroid therapy in children with pneumococcal meningitis. *Am J Dis Child* 1991;**145**:1374–8.
24 Sapolsky R, Pulsinelli WA. Glucocorticoids potentiate ischemic injury to neurons. *Science* 1985;**225**:1397–400.
25 Syrogiannopoulos GA, Hansen EJ, Erwin EL, *et al*. Haemophilus influenzae type b oligosaccharide induces meningeal inflammation. *J Infect Dis* 1988;**157**:237–44.
26 Tuomanen E, Liu H, Hengstler B, Zak O, Tomasz A. The induction of meningeal inflammation by components of the pneumococcal cell wall. *J Infect Dis* 1985;**151**:859–67.
27 Bhakdi S, Tranum-Jensen J. Damage to cell membranes by pore-forming bacterial cytolysins. *Progress in Allergy* 1988; **40**:1–43.
28 American Academy of Pediatrics Committee on Infectious Diseases. Dexamethasone therapy for bacterial meningitis in infants and children. *Pediatrics* 1990;**86**:130–3.

That disease again

There is no doubt that Kawasaki disease (in this journal we refer to Kawasaki disease and Down's syndrome; don't ask me why though I note that Tomisaku Kawasaki himself puts his name to the unapostrophised form) has a certain fascination for paediatricians. Is it the unusual clinical features, the diagnostic challenge, the rarity of coronary disease in paediatrics, or simply the exotic name which catches the imagination? The subject was well covered in the December 1991 issue of the *Archives* and I would hesitate to raise it again were it not for the publication in *Pediatrics* of data about the cardiac sequelae of the disease from a very large survey in Japan by Yosikazu Nakamura and several colleagues including Dr Kawasaki (*Pediatrics* 1991;**88**:1144–7).

Between July 1982 and December 1988 no fewer than 46 864 cases of Kawasaki disease were reported in Japan. Sixteen per cent of them had cardiac sequelae at least one month after the onset (that is 'the presence of aneurysms including dilatation or stenosis of coronary artery, myocardial infarction, or valvar lesions'). Heart disease was about one and a half times as common in boys as in girls. During the 6·5 year period there was a modest decrease in the proportion of patients developing heart disease (from 16·5% to 14·2%) and a large increase in the proportion receiving gammaglobulin (from 2·5% to 54·8%). Those with cardiac sequelae had more commonly been treated with intravenous gammaglobulin probably because the treatment was given to those with serious disease. It has previously been reported that the mortality from the disease fell from 2% in 1967 to 0·1% in 1986.

This study adds to the epidemiological data about Kawasaki disease and its sequelae but provides no evidence to support or refute the use of immunoglobulin.

ARCHIVIST